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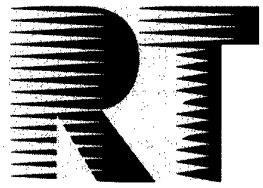


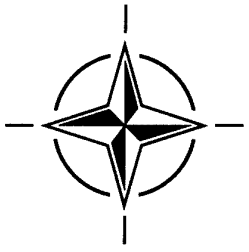
RESEARCH AND TECHNOLOGY ORGANIZATION
BP 25, 7 RUE ANCELLE, F-92201 NEUILLY-SUR-SEINE CEDEX, FRANCE

RTO MEETING PROCEEDINGS 31

Individual Differences in the Adaptability to Irregular Rest-Work Rhythms/Status of the Use of Drugs in Sleep-Wakefulness Management

(les Différences entre individus concernant les facultés d'adaptation aux rythmes irréguliers activité-repos/Le point sur l'utilisation des médicaments pour la gestion des périodes veille-sommeil)

Papers presented at the RTO Human Factors and Medicine Panel (HFM) Workshop held at the Scuola Navale Militare "Francesco Morosini" in Venice, Italy, 3-4 June 1999.



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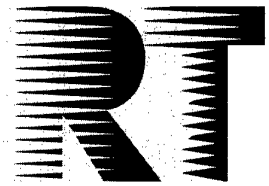

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The Research and Technology Organization (RTO) of NATO

RTO is the single focus in NATO for Defence Research and Technology activities. Its mission is to conduct and promote cooperative research and information exchange. The objective is to support the development and effective use of national defence research and technology and to meet the military needs of the Alliance, to maintain a technological lead, and to provide advice to NATO and national decision makers. The RTO performs its mission with the support of an extensive network of national experts. It also ensures effective coordination with other NATO bodies involved in R&T activities.

RTO reports both to the Military Committee of NATO and to the Conference of National Armament Directors. It comprises a Research and Technology Board (RTB) as the highest level of national representation and the Research and Technology Agency (RTA), a dedicated staff with its headquarters in Neuilly, near Paris, France. In order to facilitate contacts with the military users and other NATO activities, a small part of the RTA staff is located in NATO Headquarters in Brussels. The Brussels staff also coordinates RTO's cooperation with nations in Middle and Eastern Europe, to which RTO attaches particular importance especially as working together in the field of research is one of the more promising areas of initial cooperation.

The total spectrum of R&T activities is covered by 7 Panels, dealing with:

- SAS Studies, Analysis and Simulation
- SCI Systems Concepts and Integration
- SET Sensors and Electronics Technology
- IST Information Systems Technology
- AVT Applied Vehicle Technology
- HFM Human Factors and Medicine
- MSG Modelling and Simulation

These Panels are made up of national representatives as well as generally recognised 'world class' scientists. The Panels also provide a communication link to military users and other NATO bodies. RTO's scientific and technological work is carried out by Technical Teams, created for specific activities and with a specific duration. Such Technical Teams can organise workshops, symposia, field trials, lecture series and training courses. An important function of these Technical Teams is to ensure the continuity of the expert networks.

RTO builds upon earlier cooperation in defence research and technology as set-up under the Advisory Group for Aerospace Research and Development (AGARD) and the Defence Research Group (DRG). AGARD and the DRG share common roots in that they were both established at the initiative of Dr Theodore von Kármán, a leading aerospace scientist, who early on recognised the importance of scientific support for the Allied Armed Forces. RTO is capitalising on these common roots in order to provide the Alliance and the NATO nations with a strong scientific and technological basis that will guarantee a solid base for the future.

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Individual Differences in the Adaptability to Irregular Rest-Work Rhythms/Status of the Use of Drugs in Sleep-Wakefulness Management

(RTO MP-31)

Executive Summary

The Human Factors and Medicine Panel (HFM) of the NATO Research and Technology Organization (RTO) held a Workshop entitled "Individual Differences in the Adaptability to Irregular Rest-Work Rhythms/Status of the Use of Drugs in Sleep-Wakefulness Management" at the Scuola Navale Militare "Francesco Morosini" in Venice, Italy, 3-4 June 1999.

The Workshop was held to address both the individual difference implications during irregular sleep-wake regimens and the state of the art in the pharmacological management of sleep-wake rhythms. Wide psychophysiological differences exist in some functions not well investigated in the past: tendency to fall asleep, capability to resist sleepiness and mental fatigue, adaptability to time-zone shifts and to irregular rest-work rhythms. The flexibility and adaptability of individuals is obviously very important in modern military Contingency Operations, commonly characterized by the need for effective performance at any time of day or night. In these contexts, selected categories of drugs may be employed in operational conditions to sustain wakefulness and/or induce sleep.

The Workshop addressed a number of topics that will benefit the military, including:

- the individual difference implications in the adaptation to shift work and to new time zones; in the tendency to fall asleep; in reactions to sleep deprivation; in the ability to adapt to polyphasic rest-work schedules and to benefit from napping strategies; in sleep inertia;
- the individual difference implications in reaction to pharmacological and non-pharmacological management of the sleep-wake rhythm, such as: bright light; melatonin; hypnotics; stimulants.

The Workshop also provided useful practical recommendations with regard to pharmacological and non-pharmacological approaches to sleep-wake management. However, it was pointed out that present knowledge on individual differences in human adaptability to irregular rest-work rhythms is quite scarce. Since more accurate methodologies to select and train people to comply with irregular schedules may guarantee the welfare and the effectiveness of the NATO soldier, a multicentric international preliminary protocol aimed to extensively address the biological and psychological markers of individual adaptability to irregular rest-work rhythms has been proposed.

Les différences entre individus concernant les facultés d'adaptation aux rythmes irréguliers activité-repos/Le point sur l'utilisation des médicaments pour la gestion des périodes veille-sommeil

(RTO MP-31)

Synthèse

La commission facteurs humains et médecine (HFM) de l'Organisation pour la recherche et la technologie de l'OTAN (RTO), a organisé un atelier sur « Les différences entre individus concernant les facultés d'adaptation aux rythmes irréguliers activité-repos/Le point sur l'utilisation des médicaments pour la gestion des périodes veille-sommeil » à la Scuola Navale Militare « Francesco Morosini » à Venise, en Italie, du 3 au 4 juin 1999.

L'atelier a eu pour objectif d'examiner à la fois l'incidence des différences entre individus au cours de cycles veille-sommeil irréguliers et l'état actuel des connaissances dans le domaine de la gestion pharmacologique des rythmes veille-sommeil. Certaines fonctions présentent des grandes différences psychophysiologiques qui n'ont pas été bien étudiées dans le passé : la tendance à s'endormir, la capacité à résister à la somnolence et à la fatigue intellectuelle, la faculté d'adaptation aux changements de fuseau horaire et aux rythmes activité-repos irréguliers. La flexibilité et la faculté d'adaptation des individus sont, évidemment, des qualités très importantes pour les opérations d'urgence militaires modernes, qui sont souvent caractérisées par la nécessité d'être très performant de jour comme de nuit. Dans ce type de situation, il est envisageable d'utiliser des catégories de médicaments spécifiques dans des conditions opérationnelles pour prolonger un état de veille et/ou pour provoquer le sommeil.

L'atelier a examiné un certain nombre de sujets susceptibles d'intéresser les militaires, dont :

- L'incidence des différences entre individus sur l'adaptation au travail par équipes et aux nouveaux fuseaux horaires; sur la tendance à somnoler; sur les réactions au manque de sommeil; sur la faculté d'adaptation aux cycles d'activité/repos polyphasiques, sur les profits à tirer de siestes planifiées; et sur l'inertie provoquée par le sommeil.
- l'incidence des différences entre individus sur les réactions à la gestion pharmacologique et non pharmacologique des rythmes veille/sommeil, telles que : la lumière forte; la mélatonine; les hypnotiques et les stimulants.

L'atelier a également fourni des recommandations pratiques concernant les approches pharmacologiques et non pharmacologiques de la gestion des cycles de veille/sommeil. Cependant, il a été précisé que très peu d'informations sont disponibles sur les différences entre individus concernant la faculté d'adaptation aux rythmes activité-repos. Etant donné que des méthodologies plus précises pour la sélection et l'entraînement des équipages adaptées aux horaires irréguliers pourraient garantir le bien-être et l'efficacité des troupes de l'OTAN, il a été proposé d'établir un projet de protocole international multicentrique en vue d'étudier en détail les marqueurs biologiques et psychologiques de la faculté d'adaptation aux rythmes irréguliers activité/repos.

Contents

† Paper not available at time of printing

Preface

Contingency Operations (peacekeeping, humanitarian aid, peace enforcement, full scale offensive operations) in NATO provide new challenges to military personnel's health, safety and performance. In fact, these operations are commonly characterized by the need for effective performance at any time of the day or night, consequently involving sleep deprivation and fragmentation, rapid troop deployment across different time-zones, inversion of sleep-wakefulness rhythms, sleepiness on the job, and performance degradation due to fatigue.

There is a growing body of knowledge pointing to the existence of important individual psychophysiological differences that may enable some individuals to better adapt to irregular rest-work rhythms. Furthermore, selected categories of drugs may be employed in operational conditions; individual compliance to drugs acting on sleep and wakefulness needs specific evaluation protocols. The purpose of this Workshop was to address both the individual difference implications during irregular sleep-wake regimens and the state of the art in the pharmacological management of sleep-wake rhythms.

Topics addressed include:

- individual difference implications in:
    1. sustained and continuous operations
    2. flash adaptation to shift work and to new time zones
    3. tendency to fall asleep
    4. sleep deprivation
    5. polyphasic rest-work schedules and napping strategies
    6. sleep inertia
    7. bright light therapy
    8. melatonin therapy
    9. use of hypnotics to promote sleep
    10. use of stimulants to sustain performance

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TECHNICAL EVALUATION REPORT

by

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1. INTRODUCTION

The Human Factors and Medicine Panel (HFM) of the NATO Research and Technology Organization (RTO, a merger of the former NATO Advisory Group for Aerospace Research and Development - AGARD- and the NATO Defence Research Group -DRG-) held a Workshop on "Individual Differences In The Adaptability To Irregular Rest-Work Rhythms/Status Of The Use Of Drugs In Sleep-Wakefulness Management" at the Scuola Navale Militare "Francesco Morosini" in Venice, Italy, 3-4 June 1999. The Workshop was organized by Col. ItAF Silvio Porcu' (IT) as Chairman, and Dr. Didier Lagarde (FR) and Dr. John Caldwell (USA) as Co-chairmen. The host was Navy Captain Emilio Taietta, Director of the Scuola Navale Militare "F. Morosini". The Workshop audience included experts from NATO countries as well as from invited nations. Twenty-three papers, including two key-note addresses, were presented from nine NATO countries (France, Germany, Greece, Italy, Netherlands, Norway, Poland, United Kingdom, United States of America), from two PfP countries (Lithuania, Sweden) and one non-NATO country (Israel).

2. THEME

Contingency Operations are increasingly common in NATO. They include a wide array of operations, ranging from peacekeeping and humanitarian aid to peacekeeping full scale offensive operations. Military operations providing relief from the effects of natural disasters and terrorism can also be considered as Contingency Operations. These operations usually involve the cooperation of multinational forces in hostile environments, often far from national support bases.

The prevalence of Contingency Operations in NATO provide new challenges to aircrew health, safety and performance. In fact, these operations are commonly characterized by the need for effective performance at any time of the day or night, consequently involving sleep deprivation and fragmentation, rapid troop deployment across different time-zones, inversion of sleep-wakefulness rhythms, sleepiness on the job, and performance degradation due to fatigue.

There is a growing body of knowledge coming from basic sciences, sleep-wakefulness research, chronobiology, pharmacology (use of drugs also as probes) indicating the existence of important individual differences (psychophysiological differences) in some functions not well investigated in the past: tendency to fall asleep, capability to resist sleepiness and mental fatigue, adaptability to time-zone shifts, to irregular rest-work rhythms, to monotonous tasks, to different light/dark and dietary regimens. The flexibility of individual biological clocks can also be modulated by many other factors, such as, for instance, training or motivation. Furthermore, selected categories of drugs may be employed in operational conditions; individual compliance to drugs acting on sleep and wakefulness needs specific evaluation protocols.

More accurate methodologies to select and train people to comply with irregular schedules may guarantee the welfare and the effectiveness of the NATO soldier. Papers were solicited that addressed both the individual difference implications during irregular sleep-wake regimens and the state of the art in the pharmacological management of sleep-wake rhythms.

3. PURPOSE AND SCOPE

The Workshop expected to review the acquired knowledge and emerging issues with specific regard to individual difference implications in:

- Sustained and continuous operations;
- Flash adaptation to shift work and to new time zones;
- Tendency to fall asleep;
- Sleep deprivation;
- Biological clock readjustment;

- Polyphasic rest-work schedules and napping strategies;
- Sleep inertia;
- Light therapy and melatonin therapy;
- Use of hypnotics to promote sleep and stimulants to sustain performance;
- Antagonists of benzodiazepines to counteract hypnotic effects.

The Workshop also expected to provide useful practical suggestions with regard to pharmacological and non-pharmacological approaches to sleep-wake management, and to point out the present knowledge on individual differences in human adaptability to irregular rest-work rhythms.

4. WORKSHOP PROGRAM

The Workshop was opened by General Finocchio, Italian Military National Delegate to RT Board. He spoke about the general objectives of the RTO after the merging of AGARD and DRG.

Speakers and participants were also welcomed by Colonel Silvio Porcú, who also acted as Local Coordinator.

Finally, Dr. Cornelis Wientjes, the Executive of the HFM Panel, briefly introduced the HFM Panel mission, scope and mode of operation.

The papers were arranged according to the two main topics in two Sessions, each one being preceded by a key-note address as follows:

A. Keynote address I: Hypnotics and stimulants in operational settings, by Air Commodore A. Nicholson, UK

SESSION I - Status of the use of drugs in sleep-wake management
Chairmen Session Ia: Col. S. Porcú, IT, and Med. en Chef D. Lagarde, FR
Chairmen Session Ib: Med. en Chef D. Lagarde, FR and Dr. J. Caldwell, USA

Ten papers addressed the issue.

B. Keynote address II: Individual differences in reactions to irregular work hours, by Dr. T. Akerstedt, SW

SESSION II - Individual differences in the adaptability to irregular rest-work rhythms and shift-work.
Chairmen Session IIa: Dr. T. Akerstedt, SW, Dr. J. Caldwell, USA
Chairmen Session IIb: Air Cdre A. Nicholson, UK and Col. S. Porcu', IT

Ten papers addressed the issue (although one author, Dr. Maksymiuk from Poland was not able to attend the presentation, but he sent his contribution to the Programme Committee Chairmen and it is included in the present TER and Proceedings – one paper presented by Dr Lavie, Israel, is reported in the TER but is not included in the Proceedings).

5. TECHNICAL EVALUATION

5.1 Keynote Address I

Air Commodore Anthony Nicholson, in Keynote address #1, gave a global overview of the pharmacological management of irregular sleep-wake patterns during continuous and sustained operations, based on his own long-term experience in the RAF during both the "Pre- and Post-Cold-War" era. During the Falklands war, the RAF was faced with problems coming from long duration flights, as well as from the high workload of intensive operations. In that situation, to help the crews sleep at unusual hours, they were requested to find a hypnotic with particular characteristics: rapid absorption, no residual effects, limited duration of action, peak concentration at about 1 hour. The drug of choice was Temazepam, a benzodiazepine hypnotic that has been proved to be effective and free of significant residual effects in a large number of laboratory and in-the-field studies. On the other hand, based on the results of studies carried out in his laboratory at DERA, UK, the author expressed serious reservations in using Zolpidem during military operations, especially if involving females. In fact, he found that, after Zolpidem administration before a daytime sleep, six out of nine subjects showed a strong impairment of task performance during the subsequent night; this negative effect was more pronounced in women. As regards the use of stimulants during sustained operations, the author stressed that any side-effect on the cardiovascular system must be recognized; drugs showing such effects should consequently be avoided. Nicholson reported on the results of a study on the use of Pemoline (10, 20, 30, 40 mg) or placebo during the night after a daytime sleep with Temazepam. Pemoline significantly improved nocturnal vigilance; however, after some years of use of

Pemoline in the UK, this drug is no longer allowed (although it is still used in the USA). The author believe that, although an occasional use of Pemoline could be useful, maybe caffeine should be preferred. In a study in which the author administered 300 mg of caffeine during the night associated with a daytime sleep with Temazepam, he found caffeine to be effective in sustaining performance. Nicholson concluded that in highly intensive operations the main aims must be to assure adequate sleep and maintain good levels of performance. Stimulants should be used only when strictly necessary; a synergy in the use of stimulants and hypnotics is recommended.

5.2 Status of the use of drugs in sleep-wake management (SESSION I)

Sustained and continuous operations are far more important and strategic in NATO operations during the present "Post-Cold-War" than before. Military operations have to be performed in all weather, day and night conditions. Mission effectiveness may be challenged by the stresses of long duration operations, information overload, dangerous environmental conditions, high workload and fatigue. Furthermore, extended air operations, characterized by multiple time-zone changes and irregular work schedules, will result in circadian rhythm disruption, sleep loss and fatigue. All these factors have clear detrimental effects on the possibility of maintaining high levels of performance, contributing to operational errors. The use of pharmacological aids to induce sleep and/or sustain wakefulness has a critical role in the acute shifts of the sleep-wake cycle, during night-time intensive operations and in every extreme work/rest schedule.

The papers in the first Session discussed the importance of pharmacological countermeasures in sleep-wake management. The usefulness of different hypnotics and stimulants in dealing with crew tiredness and, consequently, in minimizing performance degradation was considered.

Lagarde et al. (paper #1) provided an overview of current knowledge on Modafinil as a wake-management drug. The use of a stimulant may be required during SUSOPs or CONOPs to insure high levels of vigilance and performance. In this context, according to the authors, all drugs with known side-effects, like amphetamines, should be eliminated. In the recent past Modafinil, a new original and synthetic substance with awakening properties, has been used successfully in the treatment of narcolepsy and idiopathic hypersomnia. However, Modafinil has also been administered to healthy subjects showing strong alerting effects during periods of up to 60 hours of sleep deprivation. High levels of performance have been maintained during 48 hours of continuous wakefulness with Modafinil administration. Up to now, no side-effects have been recognized, nor negative effects on recovery sleep. In addition, this drug showed neuroprotective action in mice against a neurotoxic agent (Soman). The authors suggested using Modafinil in the military for its awakening properties. In peace time no drug should be used, except after a crash, to facilitate the waiting period between crash and rescue. In France Modafinil is available under the pilot seat. It is recommended to take 200 mg of Modafinil over 8 hours to stay awake up to 48 hours (max 4 intakes). During wartime, the use of Modafinil can be allowed only by the High Command. The Health Service can only give advice; the directions for use depends on the operational situation and are confidential. As regards individual difference implications, the authors underlined that, in healthy subjects, differences related to age or gender have never been found. Some of the rarely observed differences can be due to weight and sometimes to individual susceptibility. To avoid any negative effect, the authors recommended starting with a 100 mg dose, before the use of a full dose of Modafinil (200 mg).

J. Caldwell (#2) reported on the efficacy of Dextroamphetamine sulfate (Dexedrine) in counteracting decreased vigilance and attention of helicopter pilots in a laboratory simulation of 64 hrs of sustained operations without sleep. The repeated administration of 10-mg of Dexedrine at 0000, 0400 and 0800 significantly attenuated performance reduction as compared to placebo in most flight manoeuvres. Dexedrine also reduced the increase in theta and delta EEG activity recorded in the placebo conditions as early as after 23 hrs of wake. As regards self-reported mood and sleepiness, vigor decayed more sharply and fatigue and confusion increased more rapidly as a function of sleep loss under placebo than under Dexedrine. Finally, Dexedrine affected the quality of recovery sleep in that sleep efficiency was lower and stage 1 percentage was higher after the drug intake than after placebo. Dexedrine also reduced REM percentage and lengthened REM latency during recovery sleep as compared to placebo. Generally, there were no clinically significant side-effects due to Dexedrine, although large individual differences seem to exist. As an example, one subject showed increased diastolic blood pressure that decreased when he was retested in a prone position, while

another subject became very excitable and talkative under Dexedrine. Caldwell concluded by claiming that, even though Dexedrine can not be considered a substitute for sleep, its use in operational environments where short-term sleep deprivation of up to 64 hours is unavoidable and high levels of performance are required can indeed be supported. A follow-on study involving longer periods of continuous wakefulness was recommended.

In several operational settings, personnel may be required to sleep at unusual hours (e.g. during the daytime), and/or in difficult environmental (noisy) or psychological (under stress) conditions. In these situations, hypnotic drugs can help to deal with the above-mentioned factors. Kodounis (#3) provided an overview on the treatment of insomnia with hypnotics, with special reference to the non-benzodiazepine 3rd generation of hypnotics (zolpidem, zopiclone). After a large review of recent studies on imidazopyridines (zolpidem) and zopiclone effects on sleep and subsequent alertness and performance, Kodounis concluded that the 3rd generation hypnotics have some advantages over the older benzodiazepines, since they do not significantly impair higher cognitive functions during the day after administration. More specifically, zolpidem is free of any influence about 6 hrs after administration, while zopiclone after-effects may last longer, since it has a longer half-life (about 5 hrs Vs 2.5 hrs). From this point of view, zolpidem is to be preferred to zopiclone, although a drawback of its very short half-life is that the hypnotic effect may wane during the last part of the night, leading to a deterioration of sleep quality. As regards sleep architecture, these new hypnotics allow a good sleep quality, since they do not significantly reduce SWS and REM percentages. Kodounis also claimed that the possibility of dependence on these drugs as well as their synergistic effects with alcohol have not been adequately addressed yet. The latter point is of great importance since some observations from military Air Forces have shown that pilots may occasionally try to fight their stress with alcohol.

Griefahn and co-workers (#4) presented an experimental protocol aimed to assess the effects of extremely low frequency magnetic fields (16.7 Hz) on the production of melatonin in man. These magnetic fields are emitted by railways, to which many people (residents living near railway tracks, commuters and other employees of railway companies) are regularly exposed. The authors reviewed the literature on the effects of electromagnetic waves on melatonin synthesis both in animals and in human subjects. While animal experiments have unequivocally revealed an inhibitory effect of low frequency magnetic fields on melatonin synthesis, presumably due to the perception of magnetic fields as light by the photoreceptors of the retina, these effects in humans are debated. The authors believe that, although carefully executed, most of the recent studies on this topic are flawed by methodological problems, such as: single determinations of melatonin concentration (not taking into account the considerable interindividual differences in the temporal distribution of melatonin synthesis); unreliable information on basal melatonin production of the subjects; the questionable choice of between subject instead of within subject comparisons (not considering the large interindividual differences). For these reasons the study by Griefahn and colleagues, which was just started at the time of the Workshop, has been designed to allow within subject comparisons, and to have hourly determinations of salivary melatonin concentration, long observation periods exceeding exposure time in order to detect rebound effects, and control conditions without any exposure and with exposure to a stimulus with well-known effects on melatonin synthesis. In addition, to avoid any masking effect by the actual individual phase, a constant routine procedure has been used. Other psychophysiological measures collected during the study are: personality characteristics, subjective mood, actimetry, rectal temperature and heart rate variability.

Stone (#5) provided an overview on the topic of sleep promotion in shiftworkers and intercontinental travellers. In both of these populations problems of transient insomnia, problems in initiating and/or maintaining sleep, as well as sleep disruptions, are often observed. More specifically, shift workers often complain about difficulties in maintaining sleep and sleep fragmentation and shortening, especially after the night shift. On the other hand, after a westward transmeridian flight, problems maintaining sleep and earlier occurrence of REM sleep are typically reported; while after an eastward transmeridian flight, problems initiating sleep and later REM sleep occurrence are more common. The authors listed some useful interventions that can alleviate sleep problems in shiftworkers and intercontinental travellers. The first one is the environmental control. As an example, external stimuli such as light or noise should be avoided, since they disrupt sleep, increase wakefulness and decrease slow-wave sleep. The authors also reported on the influence on sleep structure of the back angle of the seat. They studied different seat inclinations (back

angle with the vertical: 40°, 53° and 72°), concluding that the larger the back angle, the better the quality of sleep. The authors also recommended avoiding caffeine and alcohol, since they negatively affect subsequent sleep. For intercontinental travellers, the intake of melatonin at certain times should also be useful. Benzodiazepines may also be used to promote sleep, although the choice of the hypnotic will depend on the direction of flight. For shiftworkers that have problems in sleeping during the day, short acting hypnotics to facilitate sleep onset can be a suitable solution; in addition, controlled napping and caffeine during the work period have been recommended.

The paper by Sicard and colleagues (#6) reviewed current policies on caffeine use in the military, and then discussed the efficacy and the potential use of slow release caffeine (SRC) formulation. In the USAF in 1995 caffeine was recommended as a stimulant for enhancing vigilance, alertness, mood or to delay sleep. However, the tablet form was not authorized. Currently, in the US Navy, caffeine is the only approved chemical for use to promote alertness in prolonged operations. No limits on caffeine intake are set, but aircrew are grounded if they present any side effects. Coffee is not restricted for French aircrew, but caffeine tablets are not approved. The authors evaluated the effects of SRC in 2 double blind, placebo controlled sleep deprivation experiments. In the first study, 12 males and 12 females took SRC 300 mg between 0000h and 0130h during a 34 hour period of sleep deprivation. Sleep latency, evaluated by MSLT, was significantly longer with SRC. Performance improvements (STRES battery) were also observed. During the recovery night, mean sleep duration, sleep onset latency and quality of sleep were not influenced by treatment. In the second study, 16 young healthy male volunteers were exposed to a 64 h sleep deprivation period, to evaluate the effects of SRC 300 mg taken every 12 h. Attentional performance was better with caffeine than with placebo from 15 to 55 hours of sleep deprivation. In addition, performance was better with SRC whatever the STRES battery task (reaction time, mathematical, memory, spatial, tracking, dual tasks) up to 45 h of sleep deprivation. Sicard concluded that the development of a new slow release caffeine formulation may optimize the caffeine consumption strategy in an operational environment. Due to its pharmacokinetic properties, SRC 300 mg is effective to maintain cognitive performance during limited (45 h) sleep deprivation. However, like an aqueous caffeine solution (coffee), SRC is not devoid of adverse effects, that are more likely to be expressed by female subjects using oral contraceptives. This sex effect may be explained by the higher sensitivity to sleep deprivation and higher circulating caffeine levels observed in female volunteers.

Wientjes and colleagues (#7) discussed a recent experiment on the effects of tyrosine on cognitive performance and blood pressure in cadets after one week of a combat training course. L-tyrosine has been shown to improve cognitive performance in healthy subjects under stressful conditions (cold or noisy environments). This amino acid is the precursor of norepinephrine and dopamine. These catecholamines play an important role in attention processes, alertness, learning, and memory. As an example, in animal studies stress-induced depletion of norepinephrine is followed by reduced explorative and motor behavior; also in humans the clonidine-induced inhibition of norepinephrine release causes an increase in the number of lapses of attention. Since laboratory studies strongly suggest that supplementation with tyrosine may be useful in reducing the cognitive, behavioral and physiological (e.g., increase of diastolic blood pressure) effects of stress exposure, the authors designed their study to assess whether L-tyrosine administration would be effective in reducing the effect of stress also in "real life" conditions. The experiment was carried out on a group of cadets of the Royal Military Academy who had to complete a combat training course as a part of their training program. This course involved sleep loss, as well as highly demanding psychological and physical conditions. L-tyrosine (2 g) was supplied in a drink containing proteins and other amino acids (phenylalanine, lysine, cysteine, arginine, etc). Experimental subjects took one drink daily for a period of five days, while a control group took a placebo drink containing carbohydrate but no protein at all. Assessment of performance and blood pressure was made prior to the combat course and on the sixth day of the course. The experimental group performed better than the control group on a memory and tracking task. In addition, tyrosine was effective in decreasing systolic blood pressure, while no effect on mood was found. Wientjes and co-workers claimed that these findings suggest the usefulness of tyrosine in reducing the effects of stress and fatigue on cognitive performance under operational circumstances characterized by high psychophysical stress. However, in the following discussion it emerged that these interesting results should have been strengthened by the use of L-tyrosine in a pure form, as well as by the

administration of a real placebo. The authors explained that the administration of tyrosine as naturally contained in food was due to restrictions imposed by the army's medical supervisor. The authors also stressed that the other amino acids contained in the drink are not precursors of norepinephrine, and that the placebo drink was assumed not to influence norepinephrine synthesis, since it did not contain any amino acid.

Simons and Valk (#8) provided an overview of the most stringent questions to be answered in the field of sleep and alertness management during military operations. In practice, the Royal Netherlands Air Force is faced with the following scenarios: missions during the night; very early missions; critical activities immediately following transmeridian flights, with consequent jet lag symptoms; sustained missions often involving shift work. All the above-mentioned situations may potentially cause impaired alertness and performance, and do require sleep management. In order to develop practical guidelines to be used by flight surgeons during mission preparation and at the deployment site, the Ministry of Defence of The Netherlands commissioned research on critical topics. The authors listed the most important issues to be addressed, such as: How do deal with inter-individual differences? As an example, people largely differ in their ability to sleep at unusual times of day and in hostile environments, as well as in their reactions to jet-lag or shift-work. Although desirable, determination of the best strategy for each individual case might not be feasible, especially during intensive operations. However, the authors believe that, by using sets of personal characteristics, the flight surgeon should be able to categorize his crewmembers into subgroups, and to determine for each group the best strategy to preserve performance and alertness during the mission. The authors stressed that individual differences should also be taken into account when planning strategic napping. In fact some subjects will not be able to nap, or remain drowsy for long periods after the nap. Other important issues to be specifically addressed in military settings are: the differential usefulness of different classes of hypnotics to induce sleep (e.g. zolpidem Vs temazepam); the use of melatonin for its chronobiotic effects; the efficacy of bright light to promote alertness during night shifts; the advantages of one type of stimulant over another (amphetamines Vs pemoline Vs modafinil Vs slow-release caffeine Vs normal caffeine).

Arendt and co-workers (#9) addressed the operational significance of acute and delayed effects of melatonin. The authors introduced the main clinical uses of melatonin: the treatment of any circadian rhythm related disorder (jet lag, shift work, delayed and advanced sleep phase syndrome), and other uses in oncology, immunology, and temperature regulation. It is well-known that melatonin shifts circadian rhythms, can entrain free-running sleep-wake cycles, induces transient sleepiness during daytime and lowers body temperature, may reduce sleep latency and increase sleep efficiency, and affects EEG. However, huge individual differences in reactions to this drug have been reported. As regards the use of melatonin for jet lag, of 12 field and simulation studies reviewed, 10 were successful. A dose-response effect has been found. It seems that the 5 mg fast release melatonin is the best choice. No significant side effects have been found, except sleepiness. As regards the use of melatonin in shift work, the authors reviewed 3 field studies, claiming that, when correctly timed, melatonin improves day sleep and alertness during night shift, and hastens circadian adaptation. The authors also stressed a strange phenomenon linked to individual reactions to the drug: melatonin can induce fragmented sleep in some individuals. The authors concluded by summarizing the outcomes of melatonin administration studies: melatonin can prevent free-running sleep-wake cycles in the majority of individuals when given daily at 2000 hrs from the first day of exposure to a dim light environment. Melatonin can, in some subjects, synchronize the sleep-wake cycle after a period of free-run; in this case, synchronization may depend on a short individual tau. In addition, melatonin appears to shorten the core temperature tau. Finally, it can hasten re-entrainment after a phase shift and is probably most effective when working in concert with other zeitgebers.

Ribeiro (#10) did not attend the Workshop and his paper was not available at the time when this TER was written, but is included in the Proceedings.

5.3 Keynote Address II

Dr. Torbjorn Akerstedt, in Key-note address #2, gave an updated overview of the knowledge on the possible influence of individual differences in reactions to irregular work hours. It is well known that the effects of irregular work hours differ greatly among individuals: some will have major problems, while others will adapt well to it. The variables that have received most attention over the years are age, gender, experience, diurnal type, sleep flexibility, circadian amplitude, and neuroticism. However, none of them have proved

to be very successful. One of the traditional and most studied factors is neuroticism. A number of studies have shown consistent relations with problems in shift work, but one of the few prospective studies showed no such relation. The author suspects that neuroticism may be a consequence of shift work, rather than the reverse. The same applies to sleep flexibility, i.e. the ability to move sleep to different times of the day. Two prospective studies have failed to find any predictive power, indicating that sleep flexibility is not a factor in tolerance of shift work. Also circadian amplitude (usually of the body temperature rhythm) does not seem to be related to difficulties in shift work. Most of the amplitude differences between individuals seem to be effects of masking by shift work. As regards gender, Akerstedt claimed that there is no difference in shift work tolerance between men and women if social responsibility is controlled for. Among the traditional factors of possible value, the author cited age. One might expect age to have a negative influence on sleepiness. However, this is not necessarily always the case. Several studies suggest that older individuals suffer less from night shift sleepiness than young. It seems, however, that several night shifts in a row raises sleepiness more in older workers. On the other hand, older individuals usually have fewer problems in relation to early morning work. It has been repeatedly shown that experience of night work is negatively related to general well-being over a number of years: reduced health tends to appear earlier in shift workers than in day workers. These data, together with the increased subjective nightshift difficulties associated with increasing age and experience, do not testify for experience as a major factor in adjustment. The author stressed that the issue, however, can only be answered definitively through a longitudinal study. There is some indication that morningness is associated with poor adjustment to shift work. However, prospective studies found no predictive power. Akersted observed that frequently morningness and age are highly correlated, so any effect of diurnal type may rather be effects of age. An additional observation is that there is a selection in shift work of evening types. Possibly, also the physical condition of the individual might be of importance to night shift sleepiness. Akerstedt also reported on several studies carried out in his laboratory. One approach has been to compare tolerants and non-tolerants, selected from a group of rapidly rotating shift workers, on a number of trait and state variables. The results showed that age, body mass index, marriage status, number of children, or diurnal type did not differentiate between the attitude groups. However, the non-tolerants reported significantly more sleepiness, less sufficient sleep, lower sleep quality, less feeling well rested, a higher need for sleep, higher sleepiness during the working week. These results clearly suggest that the most important factors behind the attitude were related to sleep and sleepiness in relation to the displaced work hours. The author concluded by pointing out that some traditional factors like personality and circadian amplitude seem to have little to do with tolerance of shift work. The same applies to gender, at least if social responsibility is controlled for. Age and also diurnal type seems more interesting, but the two are closely related. However, the major determinants of shift work tolerance probably are more linked with a general ability of coping with irregular work hours. The way an individual organizes his behavior to promote sleep may be very important, as may be the need for sleep. Akerstedt claimed that priority should be given to teaching sleep/wake optimization, rather than trying to find individuals with particular traits. His feeling was that the highly tolerant single nightshift worker would be older, have a low need for sleep, have a high sleep quality, be in good physical shape, and plan sleep strategically (using naps). If several night shifts occur in sequence, younger individuals may have an advantage.

5.4 Individual differences in the adaptability to irregular rest-work rhythms and shift-work (SESSION II)

Porcu' et al. (#11) reported on individual differences in sleep tendency and ability to sustain wakefulness. The transition from wakefulness to sleep is very complex, much more than what is reflected by a standard view (the classical definition by Rechtschaffen and Kales). The first limitation of this view is the use of a 20-30 second window, which is too large to recognize and describe a short, subtle and waxing and waning process as sleep onset is. It is possible to use alternative approaches to describe the wake-to-sleep transition: behavioral, subjective, and physiological. The authors indicated some possible improvements to be applied in the study of sleep onset: to use shorter epochs; more exhaustive EEG-EOG evaluations; and behavioral techniques that do not interfere with the process being studied. The authors also claimed that MSLT and MWT, based on the results of several experimental studies, are measures of two completely different dimensions: the ability to fall asleep and the

ability to sustain wakefulness. These abilities can be dissociated within each individual, since a subject can show a high ability to sustain wakefulness and, at the same time, a high tendency to fall asleep (short sleep latency to MSLT). Depending on the type of task (or work) to be performed, one should need people able to fall asleep very fast when allowed to sleep, or to sustain wakefulness for a long period of time, if requested to do so. However, these abilities can in part be acquired. The authors underlined that some non-pharmacological approaches (relaxation techniques, biofeedback, meditation) can be used to shorten sleep latency, specially when difficulties are related to anxiety problems. Sleep onset may also be conditioned, by means of classical conditioning procedures.

Maksymiuk and Jernajczyk (#12) were not able to attend the meeting. However, their paper was sent to the Programme Committee Chairmen before the Workshop, and addressed the issue of the usefulness of sleep records after mild head traumas to predict shift work effectiveness. Some evidence exists that a third of patients that suffered from a minor head trauma, develop a post-traumatic syndrome and half of them never return to work. It is also suspected that in early periods after the trauma patients can develop sleep disturbances. In the present paper the authors evaluated, by means of polygraphic recordings, the sleep pattern of a group of male subjects in an early period after a mild head trauma, comparing it to a control group. The results showed that in an early period after a trauma, changes in sleep architecture can be observed. The authors pointed out that the observed reduction in stage 2 in the patient group could be the result of an affected function of structures involved in NREM sleep generation (frontal and temporal lobes). In addition, a shortening of REM latency, a decrease of mean sleep cycle duration and an increase of the mean number of cycles in the patient group were observed. The authors explained these latter findings as the result of an acceleration of the brain metabolic regeneration process that follows the head trauma. They concluded by claiming that polysomnography is a sensitive tool in assessing sleep architecture changes after mild head traumas; polysomnography could help to improve the estimation of clinical patients' ability to perform shift work, since history of sleep disorders is one of the factors affecting the adaptability to shift work.

Garbarino and Nobili (#13) reported on a study aimed to assess sleepiness in a population of Italian shift-work policemen. It is well-known that sleep disorders and daytime sleepiness are the more frequent disturbances reported by shift workers. The consequences of such disturbances are particularly relevant when shift work is associated with tasks requiring high performance levels in stressful work conditions. The author underlined that this situation is constantly present in Police Force personnel. Their study was aimed to assess the prevalence of daytime sleepiness and sleep disorders and/or sleep disturbances due to the shift work condition, in the whole population of shift worker policemen of the city of Genoa, Italy. The policemen were all working fast rotating shifts. The identification of subjects with pathological sleepiness was assessed using a subjective evaluation scale (Epworth Sleepiness Scale, ESS). Then all the subjects that had ESS scores reaching the first level of pathological sleepiness were given an assisted questionnaire, to evaluate the presence of intrinsic sleep disorders. The results showed a relative high prevalence (9.9%) of excessive daytime sleepiness in the sample studied. About 50% of the sleepy subjects also showed some evidence of an intrinsic sleep disorder, even though the authors stressed that an accurate diagnosis cannot be made by the used questionnaire. Results also revealed a high prevalence of accidents in subjects with sleep disturbances. Moreover, a third of the sample with sleep disturbances reported having had an accident at work or driving as a consequence of excessive sleepiness. The authors concluded by alerting occupational health physicians to assess the presence of intrinsic sleep disorders worsening health problems, in particular in those shift workers, like policemen, engaged in dangerous and stressful tasks.

Ferrara et al. (#14) provided an overview on the relevance of sleep inertia, and related problems, for on-call readiness. Sleep inertia (SI) can be defined as a transitory period of hypovigilance and decreased performance that immediately follows awakening. The authors claimed that SI is the behavioral and cognitive face of a distinct state: the sleep-to-wake transition. This idea relies on the observation that physiological transitions are better described by sinusoidal waves, more than square-wave functions. Different physiological parameters (EEG power spectra, Event-Related Potentials, Cerebral Blood

Flow) indicate that the transition to wake needs some time to be completed (about 30-40 min). Consequently, SI has to be taken into account in sleep management during quasi-continuous operations. In fact, SI can be a real problem for people required to perform highly skilled tasks shortly after abrupt awakening. From a sleep logistic perspective, the negative effects of sleep loss must be weighed against those of SI upon awakening in case of emergency. As a consequence, one critical factor concerns SI duration and time course. The authors, having provided a review of the literature on this topic, as well as on SI modulating factors, concluded that SI lasts from 30 minutes to 2 hours. SI magnitude and duration are affected by: sleep stage at awakening (SWS awakenings have the greatest negative effects); sleep structure (high quantity of Slow-Wave Sleep exacerbates SI) and sleep deprivation (through its effects on sleep structure); type of task used (cognitive performance is more affected than motor performance). Circadian modulation of SI has not been well clarified yet. The authors concluded by listing some possible countermeasures to SI, and indicating some important open questions about SI to be addressed in the near future.

Lagarde et al. (#15) reported on an experiment, the Pegasus Operation, directed by Drs D. Lagarde and J. French, from IMASSA, Fr, and Brooks AFB, US, addressing the issue of jet lag countermeasures. The authors introduced the issue by reviewing the acute and chronic effects of jet lag syndrome, as well as the individual difference parameters (age, gender, chronobiological type) and the environmental parameters (direction of flight, noise, temperature, psychosocial environment) which can affect it. With specific regard to the study, completed in 1998, it was a real-world experiment involving 60 US military personnel flown from Texas to France, with a fast transmeridian flight of 9 hours. During such troop deployment, the jet lag effects interact with fatigue and sleep deprivation effects. In this study, subjective and objective vigilance, physical and cognitive performance, and several hormonal and psychophysiological parameters were evaluated (140 variables were considered). These parameters were evaluated during 3 periods: baseline (2 days), flight (9 hours) and post-flight (10 days). The authors also evaluated the use of Slow-Release Caffeine, Melatonin and placebo, taken daily for 5 days, as counter-measures to jet-lag. Forty-six parameters out of 140 were disturbed in the placebo group; there was no global influence of gender, and subjects under 35 of age reacted better than older ones. The authors recommended no specific countermeasure to jet lag between 20 and 45 of age. After middle age, especially for females, it is useful to take some pharmacological aid. To stay awake, light, social activities, physical exercise and slow-release caffeine are recommended. To facilitate recovery sleep, the authors stressed avoiding naps before going to bed, choosing a comfortable place to sleep, and taking Zolpidem if needed. Finally, in operational settings it was recommended to avoid melatonin intake, and not drinking too much coffee or alcohol.

Lavie (#16) (paper not included in the Proceedings) provided an overview of the main findings by his own laboratory on individual differences in circadian and ultradian rhythms. To measure the subtle changes of sleep propensity during 24 hours, the author developed the so-called 7/13 paradigm several years ago. This ultra-short sleep-wake rhythm, consisting of 7 minutes in bed (sleep allowed) and 13 min of wakefulness, has been applied in many different experimental conditions. The author claimed that the data from several experiments converge in indicating the existence of a "sleep gate" (a period during which the probability to fall asleep are maximal) between 0100 and 0400 a.m. Another smaller sleep gate is present in the afternoon, around 0200-0300 p.m. In addition, a period during which sleep almost never occurs has also been shown between 0500 and 0900 p.m., and called "the forbidden zone for sleep". The author stressed that the objective data (sleep recordings) are paralleled by the subjective and performance data indicating the existence of the above-mentioned pattern of gates opening-closing. The author stressed that different subjects show very different patterns of sleep and wake during the 7/13 paradigm, as well as different timing of the gates and different sharpness of the increase of sleepiness when the gates open; however, the individual patterns are very "internally consistent", each subject showing the same pattern over time. Some pharmacological approaches, such as the use of antagonists of benzodiazepines, confirmed that the basic structure of the pattern remains unchanged, although the drug modifies the amplitude of circadian alternation of sleep and wake. The pattern of gates opening-closing is also modified by age and light exposure. The author concluded by proposing a "somnotypology", defined by two interacting dimensions: morningness-eveningness, and alert-

sleepy. The morning types show a very sharp opening of the sleep gate, while the evening types have a less sharp opening of the gate and a more fragmented pattern of sleep and wake. On the other hand, alert and sleepy differ in the amplitude of the rhythm, and in the rapidity of the wake-sleep transition. These characteristics are very stable.

Kerkhof (#17) was not able to attend the Workshop. His paper is not included in the Proceedings.

Griefahn et al. (#18) reported on an experimental approach to the adaptability to shift work that will be carried out at the Institute for Occupational Physiology at the University of Dortmund. The project, still in the planning stage, aims to clarify the individual ability to adapt to night shift. Another goal is to establish whether and by which tests this ability can be diagnosed during medical occupational examinations. Based on the literature on the adaptation to shiftwork, the authors hypothesize that persons with late circadian phase and low amplitude of rectal temperature (evening types) produce less melatonin and adapt better to shiftwork than persons with early circadian phase (morning types).The project will be executed in four steps. Step 1 is a pilot study aimed at the determination of the relationship between the subjective circadian phase and the amount of melatonin production during the night. The specific hypothesis is that a late subjective circadian phase is associated with a late melatonin peak and low melatonin production. Step 2 is a constant routine study performed to examine the relationship between the subjective circadian phase and the course and amplitude of rectal temperature and of melatonin production during the 24 hours. It is hypothesized that the course and amplitude of core temperature are closely related to the course and peak of melatonin production, and with the self-rated circadian phase. Step 3 is an experimental shiftwork study planned to elucidate the role of individual characteristics for the adaptability to nightwork under strictly controlled laboratory conditions. The authors hypothesize that some individual features (circadian phase; course and amplitude of core temperature and of melatonin production) determine the ability/inability to adapt to shiftwork. These features will determine a resistance to adapt even in the case of facilitating measures. Step 4 is a prospective study aimed to clarify whether the individual adaptability to night shift can be predicted on the basis of individual features, with the hypothesis that these features are reliable predictors for the adaptability to shiftwork.

One of the most important issues in sleep management concerns the implementation of a napping regimen in a continuous operation scenario. L. Caldwell (#19) provided a review of the literature on this topic, and also presented data on the effects of a prophylactic nap on performance, sleepiness and mood during an extended work schedule. L. Caldwell claimed that abundant evidence indicates that a nap taken during long periods of otherwise continuous wake is beneficial for improving alertness and performance. However, several factors have to be carefully considered before scheduling a napping regime. One important factor is nap timing; naps should be placed at optimal times with regard to the amount of sleep loss, avoiding long periods of accumulated wake. Prophylactic naps have also been found to be very effective. Other factors to be considered are: nap length, nap placement with respect to the circadian phase of sleepiness and/or body temperature, and sleep inertia that will occur upon awakening. In her study L. Caldwell assessed whether a 2-hour prophylactic nap would affect the performance, sleepiness and mood of aviators during a 38-hour period of continuous work. Another question was whether 10-mg zolpidem could be effectively used to promote naps, since sleep was allowed at unusual hours (9 p.m.). Results indicated that both placebo and zolpidem naps were superior to a forced-rest condition in sustaining alertness. Moreover, zolpidem provided a shorter sleep latency and a longer sleep duration than placebo. Subjective and objective (RTSW) alertness was the greatest after zolpidem naps, and postnap inertia was not significantly different between the two nap conditions. Prophylactic napping also attenuated cognitive performance decrease during sleep deprivation. L. Caldwell concluded that zolpidem, a fast acting hypnotic, can be useful in situations were only a short period of sleep is allowed, since it shortened sleep onset and lengthened sleep duration. However, whether zolpidem-induced or natural naps are used, enough time from awakening should be allowed to avoid sleep inertia effects. Finally, there may be some minor effects up to 5.5 hours post-dose, although their practical impact is probably negligible.

Opstad (#20) reported on a study carried out on a group of cadets of the Norwegian Army during a Military Training Course. The course lasted

between five and seven days and was very stressful, involving strong and long lasting physical exercise, sleep deprivation and exposure to a very cold environment during the night. Subjective, objective and neurological data were collected. The author stressed that memory performance showed clear decreases right from the second day of the course, and was 80% below the baseline levels on the fifth day.

In the last communication (#21) Porcu' and co-workers presented a preliminary protocol aimed to study biological and psychological markers of individual adaptability to irregular rest-work rhythms. In the near future, a strategy to select people with the most useful psychophysiological and chronobiological characteristics to adapt to irregular work hours could be very important. The author stressed that, up to now, poor attention has been paid to the influence of individual differences in the adaptability to SUSOPs and desynchronosis (irregular/unusual rest-activity schedules, shift work, jet lag). Studies on individual differences are necessarily long, time consuming and require a large sample size. In addition, if the goal is to define the "adaptability dimension", a large number of psychological, behavioral, physiological and chronobiological variables must be taken into account, using a multivariate statistical approach. To carry out such statistical analysis, a huge sample of subjects is needed: in fact, about 12 observations for each considered variable are required. Studies of this size can hardly be carried out by a single laboratory. Consequently, the authors proposed a multicentric approach: several nations should participate to a common "core" project, sharing the subject sample size and following the same experimental paradigm. The proposed study should be carried out on healthy males working on polyphasic rest-activity rhythms. The Project is divided into 4 Phases. During Phase 1, to be carried out in the lab, the subjects are screened for individual psycho-physiological traits (sleepiness, circadian typology, extraversion, neuroticism etc.). In addition, sleep polygraphy, diurnal and nocturnal vigilance (MWT, MSLT), performance and some biological parameters (cortisol, melatonin, body temperature, EKG, etc.) will be repeatedly assessed. During Phase 2, to be carried out after 1 month of polyphasic activity, "in-the-field" ambulatory polygraphic recordings during 4 consecutive days (2 days on duty, 2 days off) will be carried out. Performance and subjective evaluations of mood will also be collected. In this phase, a blind counterbalanced administration of bright and dim light will also be provided. During Phase 3, carried out after 6 months of polyphasic activity, the same experimental design as in Ph. 2 will be followed, in order to assess possible changes in the considered variables due to an improved adaptation to the irregular rest-work schedule. Finally, during Phase 4, carried out after 7 months of polyphasic activity, the same experimental design as in Ph. 1 will be followed, on two groups of subjects selected for their "extreme" characteristics of adaptability to the irregular rest-work schedule (i.e. the best and worst adapted). During the discussion that followed the presentation, several authors expressed their interest in cooperating in the experimental protocol; the next step will be to formalize this collaboration and to assure research funding.

Varoneckas (#22) reported on a study in progress focused on the analysis of heart rate variability (HRV) during sleep as a tool for the assessment of cardiovascular adaptability and fatigue. It is well known that night sleep induces modifications in the functional state of the autonomic nervous system, and consequently in the control of heart rate as well as in hemodynamics. Sleep may have a restorative function towards the cardiovascular function, and can be used as a natural setting for cardiovascular testing without exercise involvement. Because of the changes in heart rate and HRV during sleep stages, the latter can be evaluated on the basis of the HRV pattern. Moreover, HRV might be used as a measure of cardiovascular adaptability and physical fitness. The aim of the study is the assessment of cardiovascular adaptability and fatigue based on computer analysis (non-linear dynamics, Poincaré map) of heart rate data collected during sleep, as well as during physical testing in wakefulness. The sample of subjects included healthy males with different baseline levels of physical fitness, as well as coronary disease patients. Preliminary results showed that, in healthy subjects, heart rate modifications during sleep depend on the baseline level of autonomic control and physical fitness. More expressed HRV changes during sleep and maximal heart rate response to active orthostatic test were observed in subjects showing high work load (more 900 KGm/min), as compared with those demonstrating low work load (600-900 KGm/ min) during bicycle ergometry. In healthy Ss a restoration of the cardiovascular function was principally achieved through decreased heart rate frequency. The author concluded that the alteration in maximal heart rate response to active an orthostatic test at evening time and morning time might be seen as an

indicator of cardiovascular reserve, while heart rate and hemodynamics changes during individual sleep stages might be helpful in understanding the mechanisms involved. Altogether, the test used enables an evaluation of the total level of adaptation reserve of the cardiovascular function, using the heart rate responses.

6. CONCLUSIONS and RECOMMENDATIONS

As far as the use of drugs in sleep-wake management is concerned, some important milestones have been identified in the Workshop. In selected operational settings, hypnotics like Temazepam or Zolpidem may be safely used with the rationale of avoiding the detrimental effects on performance due to sleep loss. In fact, situational insomnia (caused, for example, by anxiety due to military operations or external environmental factors) or sleep debt due to irregular hours of sleep (night operations, shift work, jet lag) can lead in a few days to cumulative negative effects on performance and on operational effectiveness and safety. From a sleep logistic perspective, it must be borne in mind that the desired advantages at the individual level (fatigue and sleep debt recovery obtained by sleep induced by hypnotics) are necessarily associated with an incapacitation of the subjects during the period of the drug effect. Moreover, side-effects and possible idiosyncratic reactions must be taken into account.

Regarding the operational use of stimulants, they may have an important role to sustain performance (mainly when combined in a complementary way with hypnotics, respectively preserving vigilance levels and promoting sleep). The development of new slow-release caffeine formulations may optimize the caffeine intake strategy in operational environments. The activating effects of tyrosine on higher cognitive processes during sleep deprivation are also promising, although further investigation is needed. Pemoline, even if it significantly improves nocturnal vigilance in laboratory and operational settings, is not allowed in some countries due to its side-effects. Amphetamines, despite concerns about their adverse effects on mood and the cardiovascular system and constraints imposed by medico-legal regulations on handling, have been successfully used for short periods of time in many operational settings (go-pills), apparently without significant negative effects. Modafinil shows the most interesting properties in terms of pharmacodynamic effects and safety. In fact, up to now no side-effects have been recognized, nor negative effects on recovery sleep. However, also in this case, further studies are needed to establish the most useful schedule of administration (dose, time) and possible long-term effects.

The majority of laboratory and field studies on the use of melatonin in counteracting jet lag and shift work effects showed its effectiveness; it seems that the 5 mg fast release melatonin is the best choice. However, huge individual differences in reactions to this drug have been reported. The critical factor is the correct timing of melatonin administration (the time of the biological clock of the subject). The use of melatonin in air crews should be very cautious.

It has been clearly shown that the effects of irregular work hours greatly differ among individuals. Some recent prospective studies have indicated that the traditional individual factors like age, gender, experience, diurnal type, circadian amplitude, and neuroticism have scarce predictive power in terms of adaptability to shift work. The major determinants of shift work tolerance are probably linked to a general ability of coping with irregular work hours. The way an individual organizes his behavior to promote sleep may be very important, as may be the need for sleep (sleep flexibility). The concept of "somnotypology" (defined by the two interacting dimensions: morningness-eveningness, and alert-sleepy), also seems to be very promising, since the individual pattern of sleep tendency at different times of day is "internally consistent", each subject showing the same pattern over time.

However, at present the available knowledge does not allow us to define univocal practical guidelines to select and train people to adapt to irregular rest-work rhythms. The final answers to the open questions on biological and psychological markers of individual adaptability to irregular rest-work rhythms can only come from a multinational coordinated effort on a common research project using a multivariate statistical approach on many variables. The core aspects of such a common project is reported in the concluding presentation of the Workshop.

Hypnotics and Stimulants in Operational Settings

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INTRODUCTION

Hypnotics and stimulants can only be used effectively in operational settings when there exists a clear understanding of the projected scenario and of the capability of the forces involved. It must be appreciated that hypnotics and/or stimulants are only likely to be used in intensive and sustained operations, and that the reason for their use is to enhance performance beyond normally expected limits in circumstances which will be extremely demanding. It is essential to identify within a projected scenario when hypnotics and/or stimulants may be useful, and, at least as far as air operations are concerned, this will ensure that drugs are used effectively. In this paper the background to the use of drugs in support of military air operations in the United Kingdom is explored, and current issues in the selection of appropriate agents and how they can be used are discussed.

WORLD WIDE TRANSPORT OPERATIONS

As far as the United Kingdom is concerned, the planned use of drugs to enhance air capability dates from the operation to regain sovereignty of the Falkland Islands in 1982 (1). A careful assessment of the intended scenario led to the conclusion that the long range operations, both transport and reconnaissance, would demand of individual crews work patterns which would imply serious sleep disruption and sleep loss. The work patterns were to be particularly onerous as, in the absence of a forward operating base, the only option was to use Ascension Island as a staging airfield. Ascension Island is almost exactly halfway between the United Kingdom and the Falklands which are 7000 miles apart. Operations to and from Ascension Island would be accomplished easily, but the onward support of the Task Force in the absence of a forward operating airfield would require return flights from Ascension Island of up to 6800 miles (Fig 1). The Campaign posed two aeromedical problems; flights would be of very long duration and intensive rates of work would be demanded to meet the projected scenario.

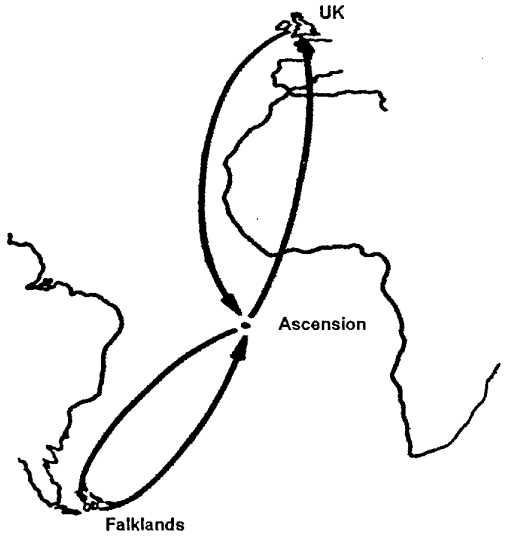

Fig 1 Staging the long range transport operations in the South Atlantic Campaign.

Prior to the South Atlantic Campaign, during the 1970s, studies had been carried out on long range missions from the United Kingdom. They had involved several exercises with transport aircraft (2). These suggested that, with some augmentation of

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the crew, the duration of individual flights could be extended to thirty hours – even though sleep would be lost over two consecutive nights. However, there was little or no information available, at that time, on how many flights could be operated over several weeks. Information from world-wide east-west civil transport operations only provided some idea of workloads which were compatible with an acceptable sleep pattern (3). These studies showed that coping with irregular patterns of work and rest had a deleterious effect on the rate of working, and that feasible rates of work were not linearly related to the days of the scenario, but fell off fairly rapidly (Fig 2). Essentially, an exponential relationship exists which in broad terms indicates that in operations involving irregularity of work and rest crews can maintain an adequate sleep pattern as long as duty hours (ie flying hours plus briefings) do not exceed 55 hours in 7 days, 75 hours in 14 days, 95 hours in 21 days and 115 hours in 28 days.

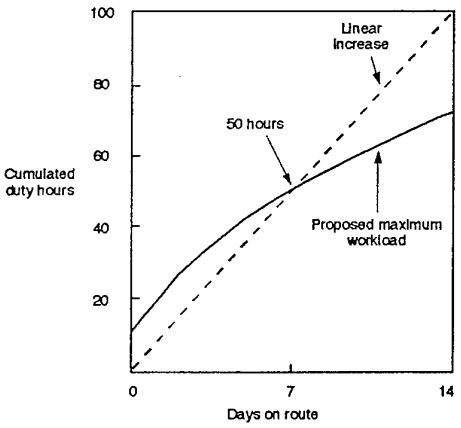

Fig 2 Rates of working with irregularity of work and rest are not linear. There is a cumulative effect which leads to a falling off in rates of working as days on the schedule proceed.

The actual work and rest pattern of a transport crew during each mission is given in Fig 3. Crews reported about midnight for the briefing and were airborne at 0300 hours. The flight was of 28 hours duration, and so was completed around 0900 hours the next day with a further couple of hours for the debrief. The crews were then able to obtain their first sleep for two nights, though it was restricted to six hours to ensure that they slept well the same night and resumed their normal sleeping pattern. Subsequent sleep was planned so that the crews would be fully rested immediately prior to the briefing for the next mission which started at midnight on Day 4/5 (Day 5 being the first day of the next cycle). With an augmented crew there was no serious concern over each individual mission.

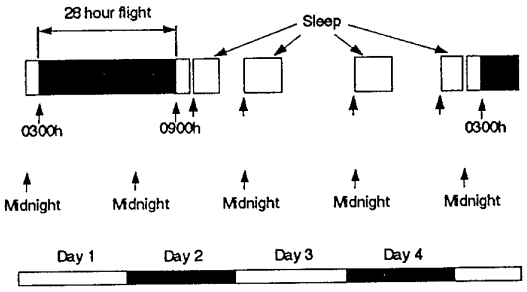

Fig 3 The work and rest pattern during individual missions.

However, the crews were expected to operate repeated missions, and prediction of workload indicated that some transport crews would be expected to fly around 150 hours in less than four weeks with estimated duty exceeding 200 hours. Some maritime reconnaisance crews would be expected to fly about 100 hours within two weeks. The maximum flying rate in peacetime for the transport crews was 120 hours per month – though this had seldom been achieved.

These projected flying hours together with the briefing and the debriefing related to each mission implied exceptionally long duty hours by any standard, and, as the Campaign developed, the necessity for these high workloads was confirmed. Transport crews operated six long-range return missions within 24 days. Each mission involved an augmented crew and extended over two nights. Over a three month period some transport crews accumulated 360 flying hours. These very long flights were made possible with air to air refuelling, and up to 14 refuelling aircraft were sometimes needed to position one aircraft in the forward operating area.

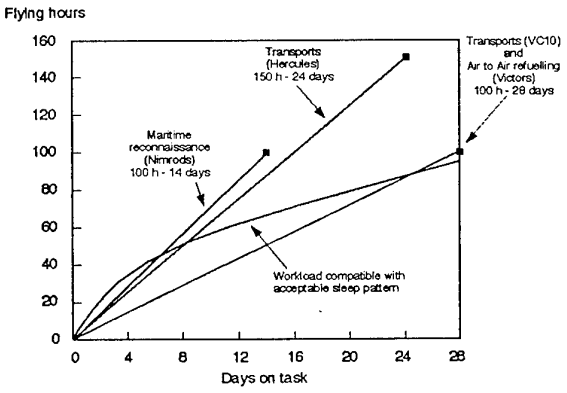

Fig 4 Flying hours attained during the South Atlantic Campaign. The duty hours believed to be compatible with an acceptable sleep pattern is indicated.

It was evident from the projected scenario that duty hours known to be compatible with an acceptable sleep pattern would be far exceeded in both the transport and maritime reconnaissance roles (Fig 4), and that sleep disturbance and sleep loss would be serious issues. It was vital, therefore, that crews would be able to sleep well during the critical rest periods especially that preceding each mission. To ensure that sleep was as good as possible during rest periods, and in the less than comfortable circumstances encountered at Ascension Island, an hypnotic was used. The lesson learned from the South Atlantic Campaign was that intensive air operations by transport and reconnaissance aircrew could be sustained over several weeks, if adequate sleep alone was assured.

IDENTIFICATION OF SUITABLE HYPNOTIC

Much work had been undertaken at the Royal Air Force Institute of Aviation Medicine during the 1970s to identify a suitable hypnotic for crews involved in intensive and sustained air operations (4,5,6 & 7). The pharmacokinetic profile proved to be crucial. Rapid absorption and limited duration of action were the key factors. These studies showed that a specific formulation of temazepam (Normison – Wyeth) was rapidly absorbed with peak plasma concentrations about 1.0 hours after ingestion, and that the dose range of 10 to 20 mg was free of any residual effects on performance 6 hours later. Freedom from residual effects within a short period of time was vital as crews were required to operate within six hours of ingestion. The particularly favourable profile of temazepam was due to the duration of action of low doses of temazepam being related to the distribution phase which has a half-life of around two hours, and that the minimum effective plasma concentration for an hypnotic effect was above plasma concentration levels which involve the elimination phase (Fig 5). This is an important point as it is not possible to predict relative duration of actions using the elimination half-life alone. The absorption and distribution phases must also be taken into consideration.

As far as the United Kingdom is concerned, temazepam (10 to 20 mg) in a rapidly absorbed formulation has, since the early 1980s, been used for aircrew. However, recently, abuse of temazepam has necessitated the introduction of legal

constraints, and this has made its prescription somewhat irksome. This is unfortunate, and so other drugs which, at present, do not have such medico-legal constraints are under consideration.

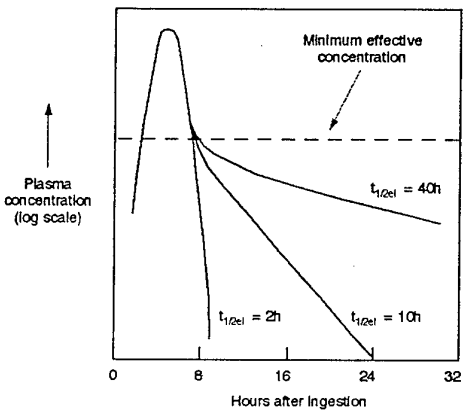

Fig 5 Duration of action is determined by the relation of the minimum effect of concentration for an hypnotic effect with the distribution and elimination phases. The Figure shows that within ingestion of single doses of diazepam (elimination half life – 40h), temazepam (elimination half life – 10h) and triazolam (elimination half life – 2h) the duration of action is related to the distribution phase and therefore independent of the elimination component.

Zolpidem is clearly an alternative (8,9). It is absorbed quickly and has a limited duration of action, and so could be useful in the critical scenario discussed in this paper. However, the question was raised several years ago when the drug was under development whether it had a particularly robust effect in women (10). The plasma concentration of zolpidem is generally higher in females with maximum concentration and mean values for area under the curve (AUC) increased by 45% and 63% respectively compared with males. This may be related to the 20% lower body weight of females.

We have, therefore, carried out a study in females to determine the usefulness of zolpidem (10 mg) in ensuring adequate sleep during an afternoon rest preceding a long period of duty overnight. They were aged between 20 and 31 years and weighed between 56 and 70kg. They ingested either placebo, zolpidem (10 mg) or temazepam (20mg) at 1315 hours and slept from 1315 to 1915 hours. Performance was measured from 2000 hours the same evening to 0800 hours the next day. After the period of sleep with zolpidem (10mg) only six of the nine subjects were able to carry out the performance tasks, and, of these, two were, at least initially, unsteady and/or emotional. The other three subjects were either incoordinated and/or nauseated and were unable to continue with the experiment. With these observations, and in view of the pharmacokinetic data, we have reservations in using zolpidem in air operations - especially with the increasing employment of women. Further studies will need to be carried out using lower doses. If a lower dose proved to be satisfactory it would imply a differential dose regime for males and females involved in shift systems - a complication not encountered with temazepam.

INTERDICTOR OPERATIONS

At the time that the Royal Air Force Institute of Aviation Medicine was concerned with the management of long range transport operations, it was also concerned with the capability of crews involved in interdictor operations – a different scenario, but certainly intensive in nature. The scenario was related to operations in Central Europe and required sorties to be generated at intervals of six hours over a period of nine days. Each squadron with an establishment of 20 aircraft was expected to maintain a

serviceability rate of 70%, and so 14 aircraft would be required to take part in each six hourly mission. With the aircrew/aircraft ratio exceeding unity this implied a random pattern of work and rest for individual aircrew.

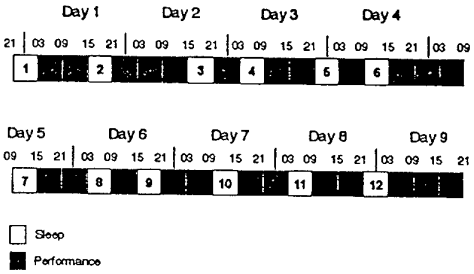

Fig 6 Simulated interdictor operation over 9 days. Rest periods of 6 hours are randomly placed, but provide an average 8 hours rest per 24 hours of the schedule. The duty periods range between 6 and 18 hours with the 18 hour duty periods allowing consecutive missions.

The pattern of work and rest which emerged from such a 9-day scenario is given in Fig 6. It was hoped that each crew could approach 12 missions over a nine day period, but if additional missions were possible by the use of drugs, then their use would be a potent force multiplier. With 15 missions the scenario would demand consecutive missions during the 18 hour duty periods. Simulations of these scenarios were carried out to determine the ability of crews to cope with such a high workload against a background of irregularity of rest (11). Sleep during the rest periods without an hypnotic varied considerably depending on the sleep history and the time of day of the rest period. However, it was concluded that, assuming all aircrew obtained sufficient sleep during the critical six hour rest periods, either naturally or with temazepam, more than 12 missions could be flown, but that performance would be seriously compromised during prolonged duty overnight which would accommodate two sorties (see Legend to Fig 7). Indeed, the lesson from these simulated interdictor missions which would involve repeated sorties over 9 days was that, even though adequate sleep may be ensured, there would be duty periods when performance would be compromised, and so the question arose whether stimulants could be used, occasionally, overnight.

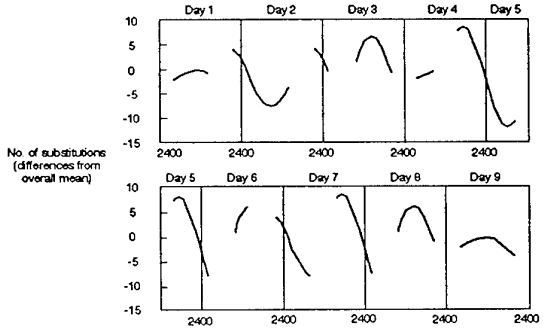

Fig 7 Predicted performance during the duty periods of a 9 day schedule simulating an interdictor operation. The model is based on data obtained from studies illustrated in Fig 6 from Reference 11. Duty overnight, which involves prolonged hours coinciding with the nadir of circadian performance, is compromised.

STIMULANTS

In considering the use of stimulants, it is essential that their pharmacokinetic and pharmacodynamic properties are taken into consideration - as has been the case with hypnotics. Certain questions need to be answered:

1. What is the mode of action of any particular stimulant in terms of modulating the transmission of central systems which control sleep and wakefulness? Should we be cautious of using drugs whose mode of action is uncertain?
2. Should the activity of the proposed stimulant be specific to the arousal system? Should we be wary of drugs which act on the noradrenergic and serotonergic transmission systems as effects on mood are unacceptable in military operations?
3. Do we have sufficient information on dose and time response?
4. Are there side effects related to the cardiovascular system?
5. Can we definitely exclude impairment of memory?
6. Do subjective and objective assessments of the effects of the stimulant coincide?
7. Does its onset and persistence of action meet the operational requirement? There may be advantages to the use of stimulants which have a slow onset of action as the purpose is not to produce an immediate effect, but to sustain performance.
8. Will the use of a stimulant be free of an alerting effect during the subsequent rest period?

The importance of these issues is illustrated by studies which have been carried out in the Centre for Human Sciences of the Defence Evaluation and Research Agency. At the recent meeting of the Aerospace Medical Association in Detroit a review of pemoline, a dopamimetic agent free of cardiovascular effects and effects on mood, in sustaining performance overnight was given based on studies by Babkoff et al (12) and Nicholson & Turner (13). Pemoline is relatively slowly absorbed and this has the advantage of sustaining performance over a long period of time. Persistence of action is dose related, and it would appear that 20mg pemoline provides the optimum balance between sustaining performance overnight and freedom from impairing sleep during the subsequent rest period – the crucial considerations in most intensive and sustained scenarios (Figs 8 and 9).

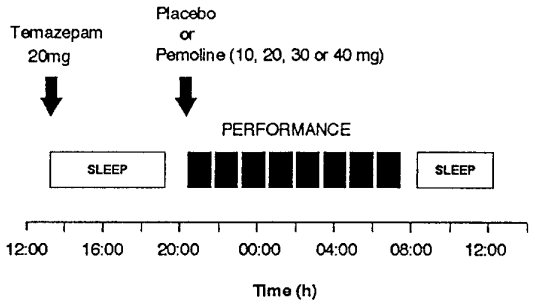

Fig 8 The usefulness of pemoline sustaining performance overnight was studied using the dose range 10 – 40mg.

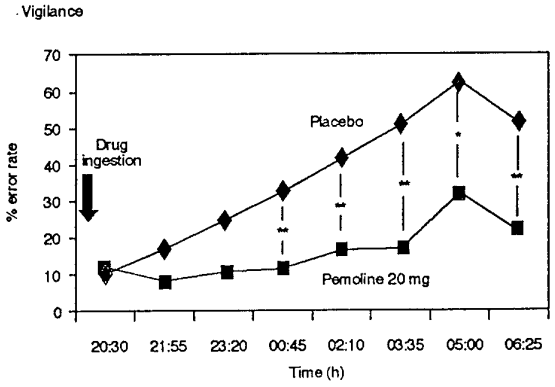

Fig 9 Pemoline (20mg) provided an optimum balance between sustaining performance without a residual effect on the subsequent sleep period.

Unfortunately, in the United Kingdom, after years of use, pemoline has been withdrawn from prescription because of hepatic toxicity in children. However, though this does not preclude its occasional use in military scenarios, restrictions on the use of pemoline in the United Kingdom together with some general reticence in the use of stimulants in military operations by individuals not familiar with the compounds is steering us towards caffeine. Indeed, in view of this and of all the considerations above, caffeine – possibly the slow release preparation - would appear to be a most promising drug for military operations.

SYNERGY OF STIMULANTS AND HYPNOTICS

There are two clear roles for hypnotics and stimulants in sustaining intensive operations – ensuring a background of adequate sleep essential to the continued effectiveness of the individual and maintaining or enhancing performance when it is likely to be degraded. Both involve a preventive approach, though with the use of stimulants it is essential to anticipate accurately when performance is likely to be impaired. Hypnotics and stimulants are effective in their own ways, but the question arises whether their use together would be more advantageous than when they are used alone.

It is in this context that studies have been carried out in the United Kingdom at the Centre for Human Sciences, Defence Evaluation and Research Agency, on the use of temazepam and caffeine together in sustaining performance overnight (Fig 10). Good sleep was ensured during the preceding rest period from 0900 to 1500 hours by using temazepam (20mg). Caffeine (300mg) was ingested midway through the 18 hour duty period at 2400 hours. With caffeine, but without the preceding use of temazepam, performance was sustained up to 0500 hours, but when

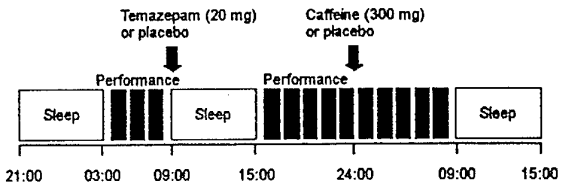

Fig 10 Potential synergy of ensuring preceding sleep with temazepam (20mg) and enhancing performance with caffeine (300mg) was studied over an 18 hour period overnight (* = p<0.05: ** p<0.01).

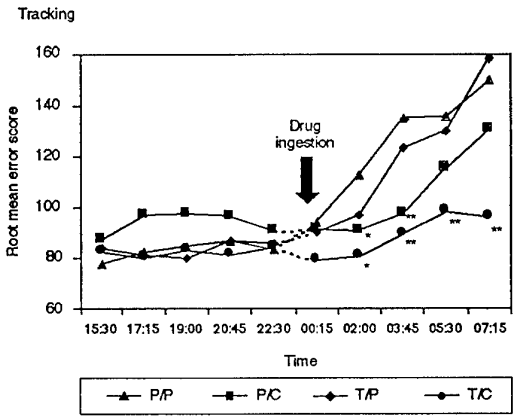

Fig 11 Performance overnight was improved with caffeine (300mg), but caffeine (300mg) preceded by sleep ensured with temazepam (20mg) improved performance throughout the overnight period (* = p<0.05: ** = p <0.01).

sleep before the duty period was ensured by temazepam the enhancement of performance with caffeine was sustained up to 0845 hours (Fig 11). Such studies emphasise the need to match drugs to the various events within an operational scenario, and the advantages of paying attention to both sleep and performance.

CONCLUSION

There are many issues involved in the use of drugs in air operations. Experience in the United Kingdom related to transport and reconnaissance operations over several weeks is that ensuring adequate sleep in all critical rest periods is essential and can have a marked force multiplying effect. Simulation studies related to interdictor operations have highlighted the beneficial effect of the use of stimulants at times when there may be an adverse juxtaposition of prolonged duty with the nadir of impaired performance associated with the circadian rhythm. It is, however, the combined use of hypnotics and stimulants which is likely to be the most beneficial when the use of stimulants can be restricted to circumstances when serious impairment of performance is likely.

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THE USE OF MODAFINIL IN OPERATIONAL SETTINGS : INDIVIDUAL DIFFERENCES IMPLICATIONS

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• ABSTRACT

Disruptions in wake-sleep rhythms, particularly induced by SUSOPS and CONOPS, are limiting factors for military personnel in operation. Pharmacological aids, such as hypnotic or stimulant substances can be effective countermeasures. Modafinil (MODIODAL®, PROVIGIL®) is a synthetic molecule prescribed for the treatment of narcolepsia and idiopathic hypersomnia. The wakening effect is potent : modafinil allows healthy volunteers to stay awake and efficient for more than 60 hours, without side effects. Its mechanism of action is complex, and it could induce wakefulness by different mechanisms, as compared with other classical vigilance enhancing drugs such as amphetamines. A neuroprotective effect against neurotoxic organophosphate agents was recently discovered. Modafinil seems to be a powerful and safe countermeasure in the management of sleep-wake rhythm during operational situations.

• INTRODUCTION

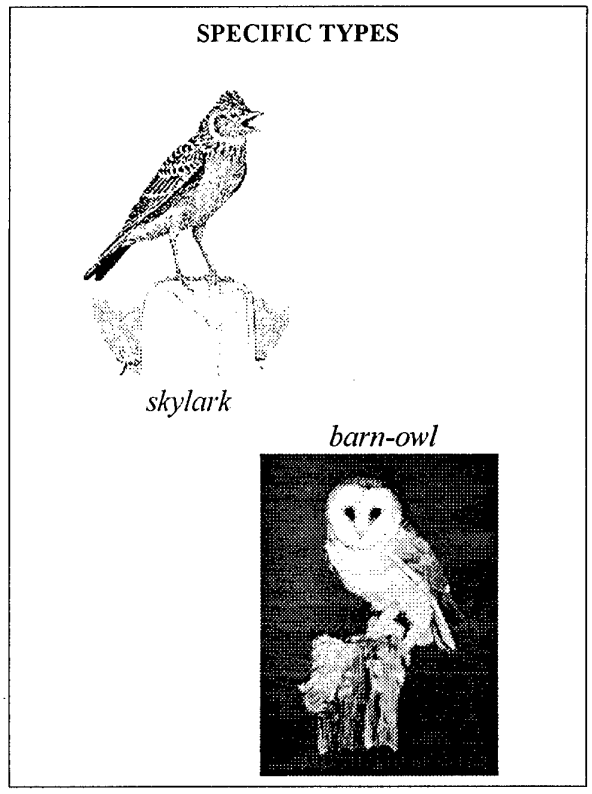
The use of drugs in sleep-wakefulness management during operational settings is changing a lot according to the fast development of new generation of psychotrops. During the second world war, the use of amphetamines was widely spread in the military personal, especially US army (16). Later during Falklands conflict, benzodiazepines were used, in a controlled maner, by the pilots of the Royal Air Force (13).

During the Persic Golf war, a new and original substance, called modafinil, was used for the first time by french military personal under a very strict medical control (while american military personal used dexedrine) (5). Before the presentation of modafinil properties, we will see why we have to use a stimulant and what kind of stimulant to use.

• THE CHOICE OF A STIMULANT

The choice of a psychotrop and especially of a stimulant to manage the vigilance come from the antinomia between physiological requirements and operational requirements.

Globally, each subject must respect his own quota of sleep, his own sleep type and his circadian rhythms. Generally, most people need between seven and eight hours of sleep. But some of them, sleep five hours or ten hours ; we called them small and big sleepers and it is an inborn characteristic. The specific type of sleep is also a physiological requirement. Some people are morningness type, it is to say that they are very operational during the morning and are out of order after 10 p.m.. We called them "skylark". On another hand, some people are eveningness type, they have the maximum of their capacity in the evening and are able to stay available and efficient very late, but they can not awake up early in the morning. We called them "barn-owl".



The result of circadian propensity to drowsiness is also very important. Everybody has two pics of drowsiness, one during the day located just after the lunch in a post-meridian period, the other during the night between 02 a.m. and 06 a.m. in the early morning. At the opposite, during the morning, around 10 a.m. and in the

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afternoon between 6 p.m. and 10 p.m., we have a top level of vigilance. This daily fluctuation is found again with the level of performance (cognitive, psychomotor and physical performance). If we repect all these physiological requirements, we will have the maximum of efficiency.

But the problem is induced by operational requirements. During sustained operations (SUSOPS) it is impossible for the soldier to sleep, sometimes during one or two consecutively days. During continuous operations (CONOPS) the soldier can sleep but not in a usual way, it is to say sometimes during the day and not during the night, sometimes two or three hours *i.e.* a disrupted sleep, and sometimes in a disturbed environment (noise, heat, light, etc...) This operational environment induces a decrease in vigilance and performance levels with fatigue, which can provoke a dramatically decrease of security and efficiency :

OPERATIONAL REQUIREMENTS

SUSOPS CONOPS	Vigilance and performance ↘
Troops deployment (transmeridian flights, sleep deprivation,...)	Security Efficiency ↘

To help the subject to maintain a good level of vigilance and performance and to preserve his security, some counter measures must be proposed. Some of them concern the physiological management with recommendations about how to take a nap or what kind of meal to eat. Others concern pharmacological management and are used when the previous one are inefficient or inapplicable. It could be substances to induce sleep (hypnotics) or substances to prolonge wakefulness.

• THE CHOICE OF AN ORIGINAL SUBSTANCE

To prolonge wakefulness, as to induce sleep, we follow a pharmacological concept which presents three main points :

- this substance has to preserve the subject from deleterious effects of sleep disturbancies,
- it can be easy to use,
- the admistration of this substance has not to induce side effects.

For these reasons, we eliminate drugs with side effects as amphetamines and amphetamine-like substances and also caffeine solution in case of repeated administration with a dose superior to 600 mg. The choice was given to a new and original wakening substance called modafinil (MODIODAL® or PROVIGIL®) studied in our laboratory since 1981 and classed by Jouvet (2) as an eugregoric substance (in greec : *eu* = good and *gregor* = wakefulness).

• THE MAIN PROPERTIES OF MODAFINIL

- Indications

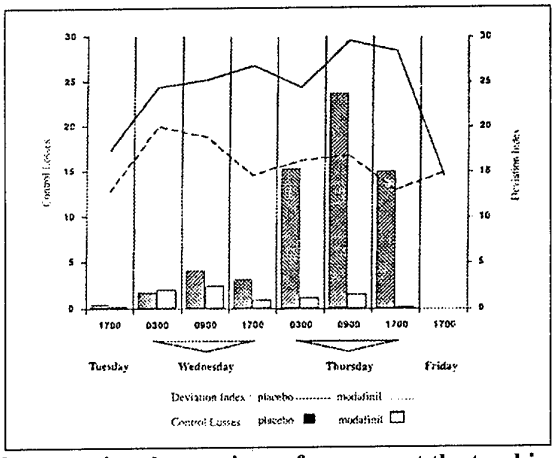
Modafinil = (diphenyl-methyl) sulfinyl-2-acetamide is a vigilance enhancing drug indicated in the treatment of narcolepsia and idiopatic hypersomnia. It is synthetized by L. LAFON laboratory (France).

- In human healthy subjects (all references are in 15)

Modafinil was also used in human healthy subjects as control population for the study of the interest of the substance in narcoleptic people : Benoit *et al.* (1987), Goldenberg *et al.* (1987), or as healthy people submitted to a sleep deprivation period : Puech and Bensimon (1987), Saletu *et al.* (1989), Lagarde *et al.* (1993, 1995a, 1995b, 1997, 1999), Bourdon *et al.* (1994), Pigeau and Buguet (1995).

- The awakening property

Modafinil presents a strong awakening effect during 60 hours of sleep deprivation. The performance is maintained at the same level than in reference period during 48 hours :



Comparative changes in performance at the tracking test under placebo and modafinil (from 7)

No side effect was found when a correct dose (200 mg) was administered every eight hours. One of the most interesting characteristic of modafinil is that it is not an anti-sleep substance but a vigilance enhancing drug. It is to say that it is possible to sleep, when the environment is available even if you took a pill, one or two hours before (3, 8). During a sleep deprivation period, this substance deletes microsleeps on EEG, increases the sleep latency (compared to placebo) and maintains the cognitive and psychomotor performance.

- The neuroprotective effect

We examined the neuroprotective effect of modafinil agonist soman-induced hippocampus damage. In mice, modafinil administered at 600 $mg.k^{-1}$ i.p. 2 hours before

soman significantly reduced the density of hippocampus ω_3 peripheral benzodiazepine binding sites, an indirect marker of neuronal damage, as compared to soman control animals. This was confirmed in rats (10). Similar results were found by another team on cerebral cortical cultures (1).

• AN ORIGINAL MECHANISM OF ACTION

The mechanism of action of modafinil is original and complex. Studies realized showed that modafinil acts as an agonist of α_1-adrenergic post-synaptic receptors (4). It binds to the dopamine uptake carrier site with low affinity (12). At high doses, pimozide can partially antagonize the behavioral and EEG effects of modafinil (6). It increases turn-over of serotonin in striatum (14), decreases cortical inhibitory aminoacids (glycin) outflow (14). It increases intracellular and decreases extracellular level of excitatory aminoacids (aspartate and glutamate), and also increases energetic pool (creatine/phosphocreatine) and decreases metabolic amino acids (14). Lin *et al.* in 1996 (11) showed that modafinil could act upon anterior hypothalamus nucleus.

To summarize it is possible to say that the α_1-adrenergic post-synaptic effects seem to be prominent ; at high doses, dopaminergic effects seem to appear. Moreover (at high doses) aminoacids neurotransmission system seems to be involved. Brain energetic effect could participate in the pharmacological action.

• THE USED PROPOSALS

Concerning only the wakening property, two kinds of attitudes are or could be adopted. In peace time : no drug must be used included training period ; the management of people must not include drug administration. One exception is the crash of helicopter or plane : to facilitate the waiting period between crash and rescue, modafinil is available in the kit located under the seat of the pilot. Like that the ejected pilot can stay awake two days to wait for the rescue.

In war time, the order to use modafinil is only given by the high command, the health service gives only advices. The directions for use depend of the operational situation and are confidential.

Concerning the individual differences implications, in healthy subjects we never found differences related to age or gender, but the differences observed concern the weight and sometimes individual susceptibility (9). To avoid these differences, a test could be done, starting with one pill (100 mg), then trying two pills (200 mg).

• CONCLUSION

Nowadays, SUSOPS and CONOPS are, unfortunately, spread all over the world. The respect of the soldier's physiology, to maintain his vigilance and performance but also his security, seems to be now taken into account ; the operational sleep management is more and more employed, because of new compounds as modafinil easy to take, very powerful and very safe. Nevertheless, their use has to be under control.

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The Efficacy of Amphetamines for 64 Hours of Sustained Operations

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Introduction

Dextroamphetamine sulfate (Dexedrine®) is a powerful central nervous system (CNS) stimulant that improves alertness and postpones the need for sleep. In aviation, where a high degree of alertness is essential during long flights, dextroamphetamine can counteract the decreased vigilance and attention, slowed reaction time, negative psychological mood, and sometimes perceptual disturbances associated with severe fatigue.

Countermeasures other than dextroamphetamine have been tested to overcome these problems, but the most popular strategy, that of emphasizing proper work/rest management, is almost impossible to successfully implement due to the unpredictability of combat operations. Other potential measures such as brief periods of exercise only temporarily reduce the negative impact of sleep loss[12, 8, 1] while exposure to cold air or noise is virtually ineffective or, in the case of loud music, actually deleterious.[9] Improving the physical fitness of personnel likewise does little to reduce the impact of sleep loss.[2]

Stimulants are more reliable for maintaining performance, especially in aviation operations where the passive nature of piloting an aircraft tends to enhance sleepiness in fatigued individuals. Of the stimulants available, dextroamphetamine (Dexedrine®) ranks favorably because its actions are known and its effectiveness has been fairly well established. Methamphetamine is similarly useful,[22, 23] but may pose a higher abuse potential. Caffeine, although easy to acquire and socially acceptable, is less effective.[18] Modafinil, a new psychostimulant, may eventually prove useful,[11] but modafinil appears to be only mildly or moderately effective in comparison to dextroamphetamine for reducing excessive sleepiness.[15]

Although the short-term efficacy of dextro-amphetamine is reasonably clear,[7, 6, 4] longer-term studies are necessary to explore whether Dexedrine can extend performance for more lengthy periods without creating problems associated with tolerance or side effects. This study sought to extend our understanding of the usefulness of dextroamphetamine beyond 40-hour periods of sustained wakefulness those requiring a total of 64 hours without sleep.

Methods

Subjects

Six UH-60 helicopter pilots resided in the U.S. Army Aeromedical Research Laboratory (USAARL) for a period of 10 days each. The mean age was 33.3 years (range was 27-40), and the mean total flight time was 1245 hours (range was 200-2700).

Apparatus

Two gelatin capsules were administered at each dose time. Each active capsule contained one 5-mg tablet of Dexedrine, and each placebo capsule contained lactose powder. *Flights* were conducted in a specially-instrumented UH-60 simulator with computer-generated visuals (set for daytime flight) and a six-degree-of-freedom motion base. *Waking electroencephalograms (EEGs)* were recorded from F_z, C_z, and P_z on a Cadwell Spectrum 32. The low and high filters were set at 0.53 and 20 Hz, respectively, and the 60 Hz notch filter was used. *Mood* was assessed with the Profile of Mood States (POMS),[14] a 65-item test which measures affect on 1) tension-anxiety, 2) depression-dejection, 3) anger-hostility, 4) vigor-activity, 5) fatigue-inertia, and 6) confusion-bewilderment. *Sleep architecture* was examined using a Nihon Kohden electroencephalograph. EEG data were recorded from C_3, C_4, O_1, and O_2 (referenced to contralateral mastoids). Electromyogram (EMG) data were recorded from under the chin. Electrooculogram (EOG) data were recorded from the outer canthus of left and right eyes (referenced to A_1). Time constants and high filter settings were: 0.3 sec. and 35 Hz for EEG, 5.0 sec. and 10 Hz for EOG, and 0.003 and 120 Hz for EMG.

Paper presented at the RTO HFM Workshop on "Individual Differences in the Adaptability to Irregular Rest-Work Rhythms/Status of the Use of Drugs in Sleep-Wakefulness Management", held in Venice, Italy, 3-4 June 1999, and published in RTO MP-31.

Procedure

Training sessions were conducted at 0900, 1300, and 1700 on Tuesday-1 (training day). On Wednesday-1 (control), Saturday-1 (recovery), and Sunday-2 (control), there were testing sessions at these times as well. On Thursday-1 and Friday-1 (the deprivation days in the first cycle), and on Monday-2 and Tuesday-2 (the deprivation days in the second cycle), testing occurred at 0100, 0500, 0900, 1300, and 1700. On these days, drug or placebo doses were administered at 0000, 0400, and 0800. The study was double blind and counterbalanced.

Flight performance

Upper-airwork maneuvers were flown both with the automatic trim system engaged (the normal mode in the UH-60) and with the trim system off (to increase pilot workload). During maneuvers, subjects were required to maintain specific flight parameters. Scores ranging from 0-100 (with 100 reflecting near perfect accuracy) were calculated based upon the extent to which subjects deviated from target values (see table 1). Individual parameter scores were averaged to produce one composite flight score for each iteration of each maneuver.

Table 1. Scoring bands for flight performance

	Maximum deviations for scores of:					
Measure (units)	100	80	60	40	20	0
Heading (degrees)	1.0	2.0	4.0	8.0	16.0 >	16.0
Altitude (feet)	8.8	17.5	35.0	70.0	140.0 >	140.0
Airspeed (knots)	1.3	2.5	5.0	10.0	20.0 >	20.0
Slip (ball widths)	0.0	0.1	0.2	0.4	0.8 >	0.8
Roll (degrees)	0.8	1.5	3.0	6.0	12.0 >	12.0
Vert. Speed (feet/m)	10.0	20.0	40.0	80.0	160.0 >	160.0
Turn Rate (degrees/s)	0.3	0.5	1.0	2.0	4.0 >	4.0

EEG evaluations

In each EEG session (15 minutes postflight), data were collected under eyes open and eyes closed. There were three iterations of eyes open/eyes closed during each session. Absolute power values were calculated for each iteration. The activity bands were: delta (1.5-3.0 Hz), theta (3.0-8.0 Hz), alpha (8.0-13.0 Hz), and beta (13.0-20.0 Hz).

POMS

The POMS was given 45 minutes after the EEG. Subjects indicated on the test form how well each of 65 mood adjectives described the way he/she was presently feeling.

Polysomnography

On each of the nights when sleep was allowed, subjects slept for approximately 8 hours while electrophysiological data (EEG, EOG, and EMG) were recorded. Standard scoring[21] yielded sleep time, minutes until the first minute of stage 2 (sleep onset), minutes from sleep onset to the first 2 minutes of rapid-eye-movement sleep (REM), the percentage of time in stages 1-4 and REM, the minutes of movement, and the percentage of time awake after sleep onset.

Results

Flight performance data

Flight performance scores under placebo versus Dexedrine during 3 baseline flights (at 0900, 1300, and 1700) and 10 deprivation flights (0100, 0500, 0900, 1300, and 1700 on deprivation days 1 and 2) were analyzed with a 3-way analysis of variance for drug, session, and iteration.

Straight and levels (SLs). A drug-by-session interaction was due to an absence of differences at baseline or the 0100 flight on the first deprivation day, which was followed by impairments under placebo relative to Dexedrine at 0500 and 1300 on day 1, and at 0100, 500, 0900, and 1300 on day 2 (see figure 1). A drug main effect was due to lower scores under placebo than Dexedrine (74.0 versus 80.1).

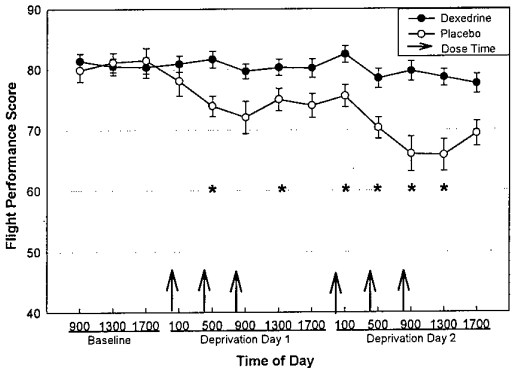

Figure 1. Straight and level flight performance

Climbs. Scores revealed a drug-by-session interaction due to decrements under placebo at 0900 and 1700 on the first deprivation day ($p<.05$) and a tendency at 0500 on the second deprivation day ($p=.0569$). There

were no effects at other times (see figure 2). A main effect on the drug factor was due to poorer performance under placebo than Dexedrine (61.6 versus 67.1).

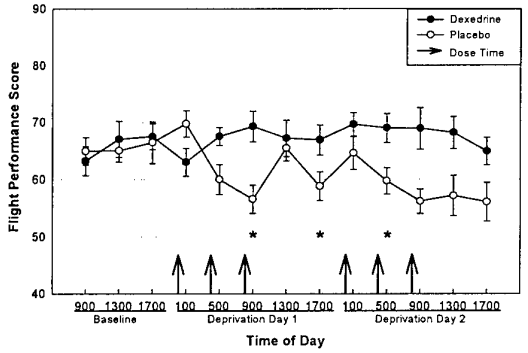

Figure 2. Climb flight performance

Descents. A drug-by-session interaction occurred because there were no differences at baseline, but performance under placebo was poorer compared to Dexedrine at 0500, 0900, 1300, and 1700 on the first deprivation day, and at 0500, 0900, and 1300 on the second day ($p \leq .05$). Performance tended to be poorer ($p=.0563$) at 1700 as well (see figure 3). A drug main effect was due to poorer performance under placebo than Dexedrine (48.8 versus 56.2).

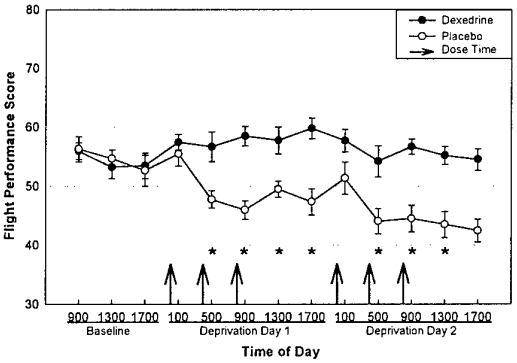

Figure 3. Descent flight performance

Left standard-rate turns. A drug-by-session interaction resulted from the absence of drug differences during baseline or at 0100, 0500, or 0900 on the first deprivation day, whereas flight control was less accurate under placebo than Dexedrine at 1300 on the first deprivation day and at 0900, 1300, and 1700 on the second day ($p<.05$). See figure 4.

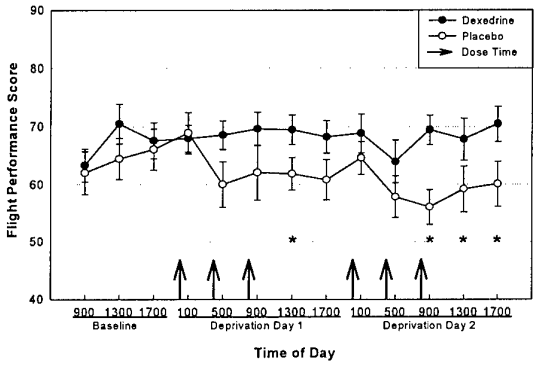

Figure 4. Left standard-rate turn performance

Right standard-rate turns. A drug-by-session interaction occurred because of the absence of differences at the predrug sessions and the first postdrug session, but poorer performance under placebo than Dexedrine at 0500 and 1700 on the first deprivation day and at 0100, 0900, and 1300 on the second day (see figure 5). A main effect was found on the drug factor because there were lower scores under placebo than Dexedrine (63.4 versus 68.2).

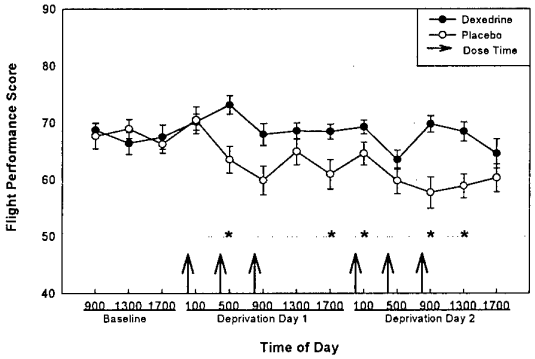

Figure 5. Right standard-rate turn performance

Left descending turn. There was a drug-by-session interaction because of no predrug differences at the 0900 and 1300 flights, but poorer performance at the end of the placebo baseline than the Dexedrine baseline ($p<.05$). Scores were then unaffected at 0100, but afterwards, scores under placebo were lower than under Dexedrine at 0500 ($p<.05$), marginally lower at 0900 ($p=.0653$), and significantly lower at 1300 ($p<.05$) on the first deprivation day. Similar differences ($p<.05$) were seen at 0500 and 0900 the next day (see figure 6).

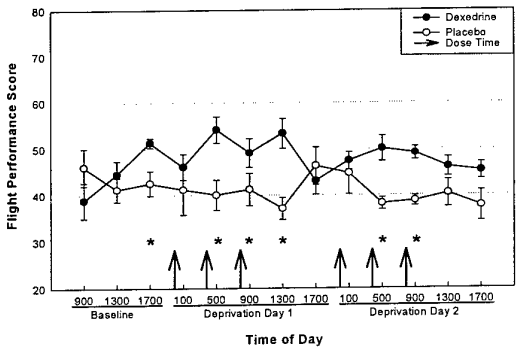

Figure 6. Left descending turn performance

Waking EEG data

Absolute power from the EEG were analyzed with ANOVAs consisting of three factors: drug (placebo versus Dexedrine), session (1015, 1415, and 1815 on baseline day; and 0215, 0615, 1015, 1415, and 1815 on deprivation days 1 and 2), and eyes (eyes open/eyes closed).

Delta activity. There were drug-by-session effects at F_z, C_z, and P_z due to more delta under placebo than Dexedrine at 0615 and 1415 on the first deprivation day, and at 0215, 1015, and 1415 on the second deprivation day. Drug main effects at F_z, C_z, and P_z were attributable to higher delta under placebo than Dexedrine. The drug-by-session effects at C_z are shown in figure 7.

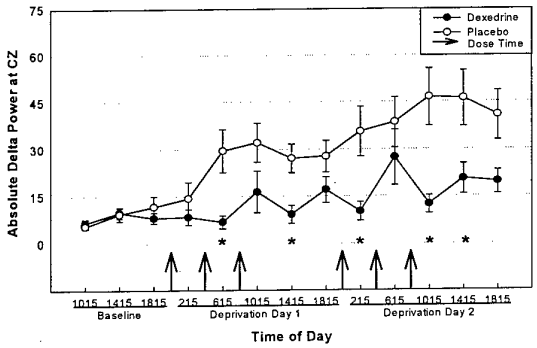

Figure 7. Absolute delta power at C_Z

Theta activity. Drug-by-session interactions at F_z, C_z, and P_z were due to increased theta under placebo compared to Dexedrine at 0615 and 1015 on the first deprivation day and at 0215 and 1415 on the second deprivation day ($p<.05$). There was a difference on the first deprivation day between the drug conditions at 1415 for F_z ($p<.05$), a marginally-significant difference at 1415 for P_z ($p=.0617$), and no difference at 1415 for C_z. On the second deprivation day, there was a difference at 1015 for F_z ($p<.05$), a marginally-significant difference for C_z ($p=.0608$), and no difference for P_z. There was a difference at 1815 for both F_z and P_z. Drug main effects were due to more theta under placebo than Dexedrine. The drug-by-session effects at C_z are shown in figure 8.

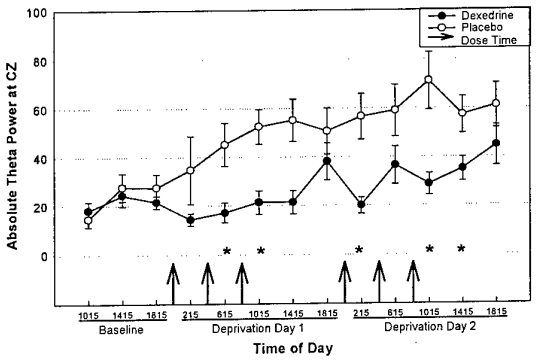

Figure 8. Absolute theta power at C_Z

Alpha activity. There was a drug-by-session interaction at F_z due to higher alpha under placebo than Dexedrine at 1415 on the baseline day (predrug), but lower alpha under placebo than Dexedrine at 0615 on the first deprivation day ($p<.05$).

Beta activity. A drug-by-session interaction at P_z was because of less beta under placebo than Dexedrine at 1815 on the first deprivation day and more beta under placebo than Dexedrine at the same time on the second deprivation day ($p<.05$).

POMS

Scores under placebo and Dexedrine at the 4 baseline sessions (1120, 1520, 1920, and 2340) and 12 deprivation sessions (0320, 0720, 1120, 1520, 1920, and 2340 on deprivation days 1 and 2) were analyzed with ANOVAs for drug and session.

Tension-anxiety and depression-dejection scales. There was only a session main effect on both of these scales. No drug-related effects occurred.

Anger-hostility scale. There was a drug main effect ($F(1,4)=9.76$, $p=.0354$) on anger-hostility scores, which reflect anger and antipathy towards others. Scores were slightly higher under placebo than Dexedrine (0.4 and 0.6, respectively).

Vigor-activity scale. A drug-by-session interaction was due to the absence of predrug differences, followed by lower vigor scores under placebo than Dexedrine at 0320, 0720, 1120, 1520, and 2340 on the first deprivation day and at 0320 on the second day ($p<.05$). There were no differences between the two after 0320 (see figure 9). A drug main effect was due to lower vigor ratings under placebo compared to Dexedrine (13.9 versus 19.6).

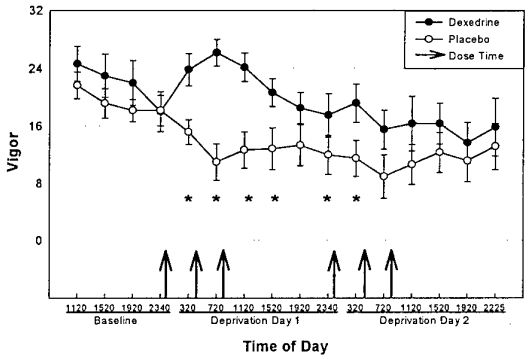

Figure 9. POMS vigor-activity scale

Fatigue-inertia scale. There was an interaction between drug and session and a main effect on the drug factor. The interaction resulted from the absence of baseline differences, followed by higher levels of fatigue under placebo than Dexedrine at 0720, 1120, and 1520 on the first deprivation day ($p<.05$). Fatigue tended to be higher under placebo than Dexedrine at 2340 ($p=.0557$). There were no differences at later times (see figure 10). The drug main effect was due to more fatigue under placebo than Dexedrine (6.5 versus 3.0).

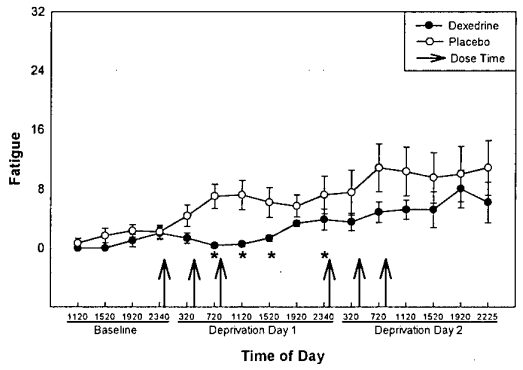

Figure 10. POMS fatigue-inertia scale

Confusion-bewilderment scale. There was a drug-by-session interaction and a drug main effect. The interaction was attributable to the lack of baseline differences, followed by higher confusion scores under placebo than Dexedrine at 1120, 1520, 1920, and 2340 on the first deprivation day and at 0720 and 1920 on the second deprivation day ($p\leq .05$) (see figure 11). The drug main effect was due to increased confusion under placebo relative to Dexedrine (4.1 versus 2.0).

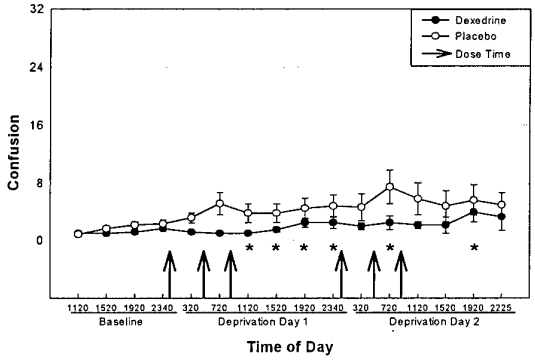

Figure 11. POMS confusion-bewilderment scale

Polysomnographic data

Data from the baseline night and the first recovery nights following Dexedrine and placebo were analyzed with a one-way ANOVA. There were differences among the days for sleep onset because of delayed sleep on baseline compared to either recovery night (the means for baseline, Dexedrine, and placebo were 8.9, 2.9, and 2.9 minutes). Sleep efficiency was higher during both recovery nights than during baseline, and higher after placebo than Dexedrine ($p<.05$). The means for baseline, Dexedrine, and placebo were 88.3, 94.1, and 96.4 percent, respectively.

The percentages of time spent in stage 1, stage 3, stage 4, and stage REM differed across the nights. There was more stage 1 during baseline than either of the recovery nights and more stage 1 during the Dexedrine recovery night than during the placebo recovery night. There was less stage 3 during baseline than the Dexedrine recovery night and more stage 3 during the Dexedrine than placebo recovery; however, the baseline and placebo recovery nights were equivalent. There was less stage 4 during baseline than the Dexedrine recovery night, but no differences elsewhere. There was more REM during the placebo than the Dexedrine recovery night, but no differences elsewhere (see figure12). REM latency was different

across the nights with the longest latency following Dexedrine. Latency also was longer during baseline than after placebo (the means for baseline, Dexedrine, and placebo were 70.6, 142.1, 37.7 minutes).

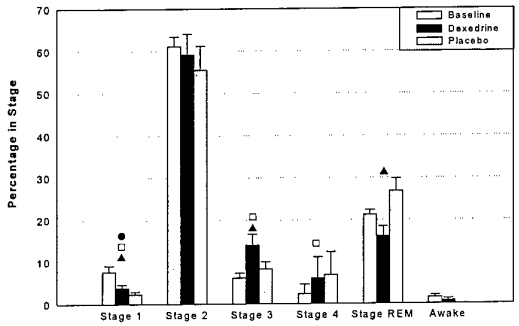

Figure 12. Sleep stage percentages (The filled circle denotes a difference between the baseline night and the placebo recovery night, the square denotes a difference between the baseline night and the Dexedrine recovery night, and the filled triangle denotes a difference between the Dexedrine and placebo recovery nights).

Discussion

This investigation extended earlier findings regarding the efficacy of Dexedrine for maintaining the performance and alertness of sleep-deprived pilots. Prophylactic administration of repeated 10 mg doses previously had been shown to attenuate the impact of sleep loss during 40 hours of wakefulness. This was particularly the case after 20 to 29 hours (0300-1200) and beyond. The present study examined whether Dexedrine would sustain performance and alertness for up to 64 hours without sleep. Flight performance was maintained by Dexedrine for up to 58 hours (the last flight of the investigation) while performance under placebo deteriorated. Dexedrine exerted the most reliable effects at 0500 and 0900 on both deprivation days. These are the times when alertness suffered the most (especially under placebo), probably due to the circadian temperature trough between 0400 and 1100. However, Dexedrine was often better than placebo at later times as well. Dexedrine attenuated performance reductions on two of the six maneuvers as early as 0100 on the second deprivation day (after 42 hours awake), on four of the maneuvers at 0500 (after 46 hours awake), on four of the maneuvers at 1300 (after 54 hours awake), and on one maneuver at 1700 (after 58 hours awake). Generally, performance under placebo declined from the first 0500 flight through the last 1700 flight. Dexedrine prevented this on all but one maneuver. These findings with 10-mg doses extend those of Pigeau et al.[20] who reported widely spaced 20-mg doses attenuated initial performance declines and recovered already-degraded performance.

Physiological indices of fatigue/alertness

A slowing of CNS activity as a function of sleep loss (especially under placebo) no doubt accounted for many of the performance decrements. Although there were numerous deprivation-related changes in the brain activity of subjects, the most pronounced were in the delta and theta bands. Slow-wave EEG activity has been found to increase as a function of sleepiness and fatigue,[19] and increased delta and theta activity are associated with performance decrements on vigilance tasks.[3] Also, increased theta power is associated with reduced speed of responding to incoming stimuli.[17] In the present case, delta and theta were elevated under placebo relative to Dexedrine as early as after 23 hours of wakefulness. Under placebo, slow-wave EEG continued to increase throughout 55 hours (and sometimes 59 hours) of deprivation. Under Dexedrine, the accentuation either was absent or the slope was noticeably reduced. Theta (and often delta) elevations under placebo relative to Dexedrine probably accounted for the inferior flight control which was most apparent after 22-26 and 42-46 hours without sleep.

Self-reported mood and sleepiness

Deteriorations in mood and alertness throughout deprivation occurred regardless of whether drug or placebo was administered. However, vigor decayed more sharply and fatigue and confusion increased more rapidly as a function of sleep loss under placebo than under Dexedrine. Drug-related differences appeared early in the deprivation cycle under placebo (after 20 hours without sleep), but under Dexedrine, ratings actually improved at this time. The decline under placebo continued for at least another 4 hours, at which time there was a leveling off, followed by a slight recovery in the afternoon of the first day. During the second deprivation day, a similar trend was observed in which vigor declined most notably after 48 hours of continuous wakefulness under placebo, whereas ratings again improved under Dexedrine. Despite the inability of Dexedrine to fully arrest *perceived* decrements in vigor, *actual* performance remained relatively constant throughout deprivation, similar to a report by Newhouse et al.[16] The absence of parallel declines in both data sets suggests subjects were aware of their

impairment, but this did not detract from their actual response capacity.

Recovery sleep

Differences between baseline and recovery nights occurred regardless of whether subjects received Dexedrine or placebo prior to recovery sleep. Sleep onset was faster and sleep quality was better after both deprivation periods than on the baseline night due to substantial sleep pressure following sleep loss. Also, there were differences in recovery sleep related to whether subjects received Dexedrine or placebo during the deprivation period. In the Dexedrine condition, subjects had received 30 mg of drug on the first day, and before this was eliminated (Dexedrine has an average half-life of 10.25 hours), the next series began. Thus, by bedtime on the second day (15 hours after the final dose), there were probably 10-15 mg of Dexedrine remaining in the participants' systems. This produced lighter sleep as well as disturbed REM sleep.

It is difficult to know whether lighter sleep after Dexedrine affected recovery since next-day performance couldn't be reliably compared (there would have been only three subjects per group); however, the size of the effects suggests that any problems would be minimal. The impact of altered REM sleep during recovery is difficult to estimate since the function of REM sleep is not fully understood.[13, 10] If it consolidates memory and/or restores mental resources, repeated use of Dexedrine might lead to progressive deterioration of higher-level thought processes. However, it seems unlikely that this would rapidly manifest itself as long as 1 night of recovery sleep is allowed after 40-hours of continuous wakefulness,[5] and 2 nights of sleep are permitted after 64-hours.

Summary and conclusions

Flight performance, physiological arousal, and mood were sustained by Dexedrine throughout 64 hours of continuous wakefulness. Dexedrine's effects were most apparent, from approximately 0300 until 1200 on both days. Generally there were no clinically-significant side effects attributable to Dexedrine; however, one subject evidenced increased diastolic blood pressure that would have been cause for concern had it not decreased when he was retested in a prone position. One subject became excitable and talkative under Dexedrine, but his flight performance was better than it was under placebo.

Although there is no substitute for sleep, Dexedrine should be considered an appropriate countermeasure for use in operational environments where short-term (i.e., 64 hours) sleep deprivation is unavoidable and a high level of performance is required. However, whether Dexedrine could preserve performance in longer periods of sleep deprivation is unclear. A follow-on study involving 112 hours of deprivation is recommended.

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Non Benzodiazepines Hypnotics: Another Way to Induce Sleep

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Summary :

The third generation hypnotics, zolpidem and zopiclone can be used to optimize rest periods during sustained operations and help the military personnel.
This is possible because these drugs provide a good quality of sleep, without residual effects in the morning after administration.
A literature review of the possible limitations of use of these drugs in pilots has been presented.

1. Introduction

Technological advances have improved the ability of military Air Force crews to withstand the operational demands of increased workload in a hostile environment (60). The 1986 air raids in Libya (59) and the Falklands war have shown, however, that physical and psychological fatigue of the pilots and ground support crews can reduce operational success. This is especially the case when operations take place from aircraft carriers in extreme conditions of frequent flights and little rest, including flights 24 hours a day, for long periods of time and lack of soundproof buildings.

Mc Couley (39) has claimed that crew tiredness is a common denominator of human errors responsible for accidents during the flight and that 60% of accidents happen during approach and landing procedures. One study (53) examined the relationship between alertness and successful landing. The results have showed that reduced alertness represents an important factor in several accidents during approach and landing. A number of studies (10) have shown that aircrews taking part in mid and long range flights have anomalies of the sleep-wakefulness cycle, which are caused by disruption of circadian rhythm. Another factor that disrupts circadian rhythms is the conduct of nocturnal operations, a current problem as the majority of NATO attacks on Yugoslavia take place in the night-time. Dealing with crew tiredness is therefore vital in accident prevention. To achieve this, it is necessary to overcome the sleep difficulties caused by operational stress, hostile environment and disruption of circadian rhythms.

Hypnotic drugs can help to deal with these difficult situations. The perfect hypnotic should act rapidly, have a short duration of action, not lead to dependence and have no residual effect so that any impairment is not carried into the next day.

It is also important to preserve the architectural structure of normal sleep. Drugs should not reduce sleep stages III and IV, which are essential for rest. They should also not interfere with R.E.M. sleep during which dreams occur, as dreams play an important role in psychological well being and are vital for effective rest.

The non-benzodiazepine 3rd generation hypnotics (zolpidem, zopiclone) are close to the above characteristics of the perfect hypnotics as existing studies prove that they preserve good sleep quality and no suppression of higher cognitive functions 6 hours after their administration.

Before reviewing the relevant literature in more detail, let us see first what exactly sleep and insomnia are. It should be noted that it is not uncommon for individuals to complain about lack of sleep and impaired daytime performance even though there is no objective evidence of insomnia from sleep recordings. This is known as pseudoinsomnia, or sleep state misperception (56).

2. Sleep and Insomnia

Even though we spend more time sleeping than in any other activity, it is difficult to define exactly what sleep is and what precise purpose it serves. We experience sleep as a loss of consciousness of our environment and we feel intuitively that it must fulfil some restorative function. Many circadian rhythms are linked tightly to our sleep/wake cycle. An adequate period of sleep at night is necessary in order to feel refreshed and effective the next day. It has been demonstrated that, while we sleep, bones grow (61), cells divide (12), wounds heal (51) and that hormones, such as growth hormones, are released (67). Sleep seems to facilitate the reinforcement of long-term memory traces (18), but is associated with a general slowing of brain activity and metabolism (38).

Arousal and wakefulness seem to be related to a high level of electrical activity within the cerebral cortex (27). When this electrical activity wanes, drowsiness and sleep set in. It seems that cortical activity is maintained by stimulatory input from a structure in the brainstem called the Reticular Activating System (RAS) (27, 63). Activation of the cortex by the RAS elicits awakening and vigilance. The RAS consists of a diffuse closed

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network of excitatory and inhibitory interneurones lying along the rostrocaudal axis of the brain system. The excitatory interneurones of the RAS are believed to use glutamic acid as their neurotransmitter, and the inhibitory ones to use γ-aminobutyric acid (GABA). GABA is the principal inhibitory neurotransmitter in the central nervous system (62) and many hypnotic, sedative, anxiolytic, anti-epileptic, anti-spastic and anaesthetic drugs owe their activity to their effects on GABA-mediated neurotransmission (16).

Sleep is not a uniform process but consists of different phases, which are called sleep stages. Five are traditionally identified: I & II (light sleep), III & IV (deep sleep) and REM. During the night, several recurring sleep cycles occur, going from awake down through the first four sleep stages and back again. The deep stages III and IV, characterized by slow waves on the electroencephalogram (EEG), are considered to be the most restorative. The fifth sleep stage, REM sleep, is characterized by paradoxical EEG activity, vivid dreams, inhibited muscle tone, rapid eye movements, bursts of sympathetic activity and penile erections in males.

Although most people sleep for around seven hours each night, it is important to realize that some people function perfectly well on four hours sleep a night, whilst others require ten hours of sleep. This means that there is no normal or correct duration of sleep and thus that insomnia cannot be defined simply by a certain sleep duration. Instead, we can identify insomnia when an individual complains of not sleeping sufficiently long or well to function properly in the day.

Insomnia should be considered as a symptom of an underlying pathology, or of a change in life-style, rather than a disease in itself. Treatment should thus be directed primarily at resolving the underlying cause. Insomnia may be transient or chronic and may be characterized by difficulties in initiating or maintaining sleep. Impaired daytime functioning is the primary consequence of insomnia.

Different types of insomnia can be identified, dominated by difficulty in falling asleep, by early awakening or by multiple nocturnal awakenings.

The causes of insomnia are numerous and can be physical, such as pain or respiratory disease, psychological, such as stress or bereavement, psychiatric, such as depression or anxiety or pharmacological, such as alcoholism or benzodiazepine withdrawal (13, 24). Often, transient insomnia can be triggered by, for example, stress or illness, which then evolves into chronic insomnia, which persists even when the original trigger is removed.

Insomnia can be related to severe consequences including elevated mortality (31, 76), increased probability of having traffic accidents (1) and comorbility with psychiatric (20) and cardiovascular (22) disease. Several studies have demonstrated impaired quality of life in insomniacs (29) and there is generally a deterioration in social and professional relationships (26, 64, 11).

A major determinant of sleep quality is sleep hygiene (15). Poor sleep hygiene can trigger transient insomnia and favour the evolution of transient insomnia into chronic insomnia. The first-line treatment of insomnia should aim to improve sleep hygiene. This can be attempted by imposing regular bedtime and rising time, optimizing the sleeping environment and evening food intake, avoiding alcohol, caffeine and sugar also in the evening, as well as naps in the daytime and by taking physical exercise during the day.

3. Treatment of insomnia with hypnotics.

3.1 History

Hypnotic medication has been available since the introduction of chloral hydrate in the early nineteenth century. This was followed by the discovery and introduction of the barbiturates (1903), chlormethiazole (1958), the benzodiazepines (1961) and finally by zopiclone and zolpidem (1987/1988). All these drugs act by amplifying GABA-mediated neurotransmission in the brain.

The modern hypnotics in use today are the benzodiazepines such as (flunitrazepam, temazepam and triazolam) the cyclopyrolone zopiclone and the imidazopyridine zolpidem. These drugs are all extremely well tolerated compared to the previous generations of drugs, which had significant toxicity. In the vast majority of cases, they are the only hypnotic drugs that should be prescribed for the treatment of insomnia today. Benzodiazepines, zopiclone and zolpidem all interact with the same receptor in the brain, the α subunit of the $GABA_A$ receptor. In binding to this protein, they facilitate receptor activation by GABA (16).

3.2 The $GABA_A$ receptor: site of action of hypnotic drugs.

GABA (γ-aminobutyric acid) is the major inhibitory neurotransmitter in the mammalian central nervous system (62). It inhibits neurons by interacting with an oligomeric protein in the cell membrane, the $GABA_A$ receptor. This protein is composed of five transmembrane peptide subunits arranged in a rosette. When the $GABA_A$ receptor is activateed by GABA, the peptide subunits move apart to form an ion-permeable pore across the membrane. This pore allows the passage of chloride ions across the membrane in response to the electrical gradient, which provides a short-circuit preventing the neuron from raisin an action potential (62). The $GABA_A$ reaptor is thought to be composed of two α subunits, two β subunits and one γ subunit (34). These differ in their amino acid composition and in their function. The β subunits are responsible for binding GABA, and thus initiating receptor activation (9). The α subunits bind benzodiazepines, zopiclone and zolpidem (34). Binding of hypnotic drugs to the α subunit increases the probability of channel opening in response

to GABA, and thus facilitates GABA-mediated inhibition (65).
There are several different isoforms of each of α, β and γ subunits whose presence in the receptor determines its pharmacological and biophysical properties (77). There are six different isoforms of the α subunit, α_1 to α_6. Receptors containing any of these isoforms recognize benzodiazepines and zopiclone, but only those containing α_1 have high affinity for zolpidem (49). $GABA_A$ receptors containing α_1 subunits have been referred to as BZ_1 or ω_1 subtypes, and those containing other α subunit isoforms BZ2 or ω2. The predominant form of native $GABA_A$ receptor in the mammalian brain has α subunit composition of α_1 β_2 γ_2 (40). The functional significance of $GABA_A$ receptor heterogenity and subtype colectivity remains unknown (17).

3.3 Absorption and elimination of hypnotic drugs.

The pharmacokinetic properties of hypnotic drugs are an extremely important determinant of therapeutic efficacy (23). A good hypnotic needs to be absorbed rapidly, to penetrate the brain and trigger sleep within thirty minutes of oral absorption of the drug. Plasma levels should remain sufficiently high to have pharmacological activity throughout the night and thus prevent nocturnal awakenings. Drug levels should have fallen below pharmacologically active levels when it is time to wake up, so that there are no residual sedative effects during the day. Drugs with very short half-life do not maintain their activity throughout the night (28), and may not prevent early awakenings. It has also been suggested (mainly from experience with triazolam) that such drugs may be more likely to produce dependence (28) and behavioral side effects (58, 42) during the day than longer-acting hypnotic drugs. Hypnotics with long half-life, on the other hand, will continue to be active the next day, producing sedation and impairment of cognitive performance (25). Difficulty waking up, and a muzzy feeling on waking (benzodiazepine hangover) may be experienced.

3.4 New generation hypnotic drugs:.

A. Zolpidem

Zolpidem is an hypnotic belonging to a new chemical class, the imidazopyridines, which are structurally unrelated to benzodiazepines. Zolpidem is a selective ligand for the central omega-1 receptor subtype with a high intrisic activity and a potent hypnotic effect. It has a low affinity for ω_1 (including α_2 or α_3 subunits) and no affinity for the peripheral BZD subtype. The ω_1 and ω_2 subtypes have specific central nervous system distribution; the ω_1 subtype being predominant in the cerebellum whilst both subtypes are present in the cerebral cortex and only the ω_2 subtype is present in the spinal cord. This specific affinity of zolpidem for the W1 subtype receptor results in marked hypnotic properties with only minor anxiolytic, myorelaxant and anticonvulsant properties. Finally, zolpidem has a short elimination half life (2,5 hours) and no active metabolites, allowing a good hypnotic activity without residual effects in the morning (48).

Clinical material, involving both healthy volunteers and insomniac populations, has clearly demonstrated the hypnotic efficacy of zolpidem in daily doses ranging from 5mg to 20mg. Moreover, the sleep architecture generally remains unaffected at these dosages, apart from an enhancing effect upon slow-wave sleep (36, 41).
In two studies (69, 5) polysomnograpfic recordings showed that zolpidem and flunitrazepam (BZD) significantly shortened sleep onset latency. Zolpidem respected the overall sleep architecture, without disturbance of N-REM III and IV stages and REM sleep. Flunitrazepam significantly decreased REM sleep, slow wave sleep and increased stage II.

In a study with 1772 hospitalized insomniac patients, only 2,2% of them reported adverse events and less than 1% of them withdrew due to intolerance. 1,5% had their nightly dose reduced to 5mg/day due to adverse drug reactions. The most frequently reported were drowsiness, hangover, dizziness and nausea and nightmares and hallucinations (33). In healthy volunteers, zolpidem 10 or 20mg/day did not significantly alter respiratory parameters (35).

In a recent article (54) the author reviewed the literature to determine whether the behavioral pharmacologic profile of zolpidem also differs from that of benzodiazepines. The specific topics that are reviewed include abuse potential, tolerance producing effects and physiological dependence-producing effects. The most parsimonious conclusion is that despite its unique neuropharmacological profile, the behavioral effects of zolpidem are generally similar to those of benzodiazepines.

Another study (71) examined behavioral effects and development of physical dependence after once-daily increasing doses of zolpidem in three baboons. The conclusion was that zolpidem produced physical dependence and the severity of the withdrawal syndrome can be characterized as intermediate.
Other studies have shown that zolpidem, at a dose of 10mg, does not lead to dependence and that the side effects are rare and comparable to placebo (57, 74). It has also been shown that its pharmacokinetics are not altered by food, alcohol, caffeine and timing of administration (6).

Disturbances in psychomotor and cognitive functioning and memory have long been recognized to be associated with the use of hypnotic drugs, especially those that are eliminated slowly. Several classes of hypnotic drugs can affect next-day functioning and memory. Barbiturates, benzodiazepines and various over-the-counter drugs have all been shown to possess such properties, to varying degrees.

Next-day drowsiness or incoordination can be dangerous when performing tasks such as car driving or the operation of machinery and psychomotor impairment

may contribute to accidents. It is therefore important that hypnotic drugs should, as much as possible, be free from such undesirable "hangover" effects (69).

Morselli (43) reviewed double-blind studies involving observations made on the day after a single dose of 20mg zolpidem. Two studies included flunitrazepam as a positive control and two others triazolam. Despite using a higher dose than that currently recommended (10mg), measurements of saccadic eye movement peak velocity and repeated testing of daytime sleep latency showed that zolpidem did not affect alertness on the day after administration, although such an effect was clearly detected with the reference benzodiazepine. Next-day psychomotor function testing did not show any impairment of simple tasks. Creation time tests, digit symbol substitution tests etc.) after either zolpidem or triazolam, although a performance decrement was seen after flunitrazepam. In a more complex simulated driving test, zolpidem did not differ significantly from placebo, while triazolam measurably affected performance.

In another study (18) flunitrazepam significantly impaired attention and memory compared with zolpidem and placebo, while zolpidem did not differ from placebo the day after administration.

The more recent studies (14, 68) also reach the conclusion that, at the clinically recommended dose (10mg), zolpidem treatment appears to give rise to no, or minimal next-day effects on psychomotor and cognitive functions.

Many studies showed that zolpidem is capable of impairing both memory and psychomotor functions near the time of peak plasma concentration. These effects, behavioral and subject-rated, are similar to those of benzodiazepine hypnotics and zopiclone (55, 2).

Another study (75) concluded that there was no significant interaction between zolpidem and alcohol, which did not potentiate the performance-impairing effects of zolpidem in the time of peak plasma concentration.

The literature on this is, however, inadequate, and further research is needed to determine whether consumption of alcohol is safe in combination with 3rd generation hypnotics.

The sedative effects of 10mg of zolpidem are not antagonized be 150-300mg of caffeine in pharmacodynamic or pharmacokinetic terms (37).

Another study (72) showed that flumazenil (1,0mg) a benzodiazepine receptor antagonist, can reverse memory impairment caused by agonists of the benzodiazepine receptor, like triazolam and zolpidem.

B. Zopiclone

Zopiclone is an hypnotic with a short half-life (5 hours) which was demonstrated efficacy in sleep quality as accessed by questionnaires (46).

A number of comparative studies with benzodiazepine hypnotics, including flunitrazepam, flurazepam, nitrazepam, triazolam and temazepam, in insomniac patients have not identified significant differences in perceived sleep quality between zopiclone and the benzodiazepines (44, 70). In EEG studies, deferences between zopiclone and certain benzodiazepine hypnotics have been observed. The most important of these is that zopiclone does not appear to decrease the time spent in slow-wave sleep and in REM sleep (44, 70). In some (but by no means all) of these studies, zopiclone actually increases the time spent in these sleep phases.

Morning-after effects of zopiclone are mild compared to most BZD hypnotics (70). Subjective assessment of alertness the next morning in insomniacs generally has shown zopiclone (7,5mg) to be superior to nitrazepam (5 or 10mg), flurazepam (30mg) and flunitrazepam (1 or 2mg). Impairment of psychomotor performance after zopiclone, however, has been demonstrated objectively in some, but not all, studies in healthy volunteers (32, 7).

In a comparative study (45) with zopiclone, flunitrazepam and nitrazepam, all three drugs induced some impairment of memory, but effects were more pronounced with the two benzodiazepines and especially flunitrazepam.

The adverse events seen with zopiclone are bitter taste, dry mouth, drowsiness, dizziness, tiredness, lack of coordination, depression and headache.

We conclude that zolpidem, because of its very short half-life, has better results in measures of next-day psychomotor performance and memory than zopiclone. A drawback of the short half-life is that the hypnotic effect may wane during the night, leading to a deterioration of sleep quality towards the end of the night. A similar phenomenon has been reported for short-acting benzodiazepine hypnotics (28). In contrast, zopiclone provide significantly fewer spontaneous awakenings (52).

Caffeine moderately antagonizes the effects of triazolam and zopiclone on the psychomotor performance of healthy subjects (45). But zopiclone counteracted the effects of caffeine more easily than caffeine counteracted the decremental effects of zopiclone.

In another study (30) the authors studied the co-administration of alcohol with zopiclone and triazolam (BZD). Alcohol enhanced and prolonged the effects of both hypnotics without modifying their plasma concentrations. Drug-alcohol interactions were mainly additive though more obvious with TRZ. The hypnotics were free from residual psychomotor and cognitive effects at 8h even after the co-administration of alcohol.

In another study (4) the authors interpreted their findings as suggesting that the users of anxiolytic benzodiazepines and zopiclone were at increased risk of road-traffic accidents.

Finally there is a report (3) of physical dependence on zopiclone in individuals with depended personalities.

In this table we can see the main properties of hypnotic drugs :

	ZOLPIDEM	ZOPICLONE	BENZODIAZEPINES half life Short (TRIAZ)	Long (FLU)
1.Efficacity to induce sleep	+	+	+	+
2.Sleep quqlity	+	+	+	+
3.Anxiolytic, Myorelaxant, Anticonvulsant	-	+	++	++
4.Elimination longlife	2,5 h	5 h	1 -4 h	20 h
5.Adverse events	+	++	+++	+++
6.Spontaneous awakenings	+	-	+	-
7.Residual effects in the morning	-	+	-	++
8.Disturbances of sleep architecture	-	+/-	++	++
9.Next day pshychomotor performance	++	+	+	-
10.Caffeins antagonizes	-	+	++	++
11.Alcohol interaction	+/-	+	++	++
12.Dependence, Tolerance effects, Abuse potential	+	+	+++	++

C. Antihistamines and antidepressants.

The antihistamines do not increase total sleep time, but offer a shorter sleep latency period. Side effects of residual daytime sedation are well documented. The antidepressants have a long half-life and residual daytime effects.

D. Melatonin.

Several studies suggest that melatonin may produce behavioral sedation or facilitate objectively measured sleep, others have found no appreciable effect. There are theoretical reasons to be concerned about its use: melatonin is vasoconstrictive and has unwanted disruptive effects on reproductive endocrine function.

3.5 Hypnotic drug use in military operations.

A French study (60) examined the action of 10mg of zolpidem and 1mg of flumitrazepam compared to placebo in 12 pilots and 12 ground personnel. The subjects underwent psychomotor testing in a flight simulator and spectroscopic EEG analysis.

Sleep quality was similar after administration of zolpidem and flumitrazepam. The ground personnel who received benzodiazepines showed difficulty in walking, somnolence and lack of energy compared to those receiving zolpidem or placebo. On the contrary, no differences were found, either in self-assessments or in psychomotor testing, in pilots. This can be explained by the fact that pilots are highly motivated and therefore able to overcome certain potentially adverse factors.

The EEG analysis showed no effect of zolpidem, while those receiving benzodiazepines had a greater prevalence of slow waves, reduction of the a rhythm, and development of fast rhythms.

Other studies (66) have shown that zopiclone, zolpidem and temazepam do not influence athletic performance. A U.S. army Aeromedical Research Laboratory study (8) compared the effects of zolpidem-induced prophylactic naps and forced rest periods in prolonged work schedules. The conclusion was that zolpidem-induced naps were more effective because the subjects obtained more sleep after zolpidem administration. Post-nap grogginess persisted for about 2 hours after either the zolpidem or placebo nap, a fact which, despite the overall benefits from prophylactic naps, could compromise performance under operational conditions if insufficient time for awakening was planned.

Another study (50) concluded that zolpidem is a hypnotic which appears to cause less global impairment than benzodiazepine during peak effect, and is free of persistent performance decrement or hangover effect.

A study of the influence of daytime administration of zolpidem and triazolam on performance showed that there is no advantage of zolpidem over triazolam (63) in performance-impairing effects.

Finally, it was shown that zolpidem improved sleep quality at high altitute (4.000 meters) without affecting respiration (5).

CONCLUSIONS

It is evident from the above that 3rd generation hypnotics (zolpidem and zopiclone) do have some advantages over the older benzodiazepines, primarily because they do not significantly influence higher cognitive functions the day after the administration. Specifically, zolpidem is free of any such influence 6 hours after administration, while the same may be true of zopiclone a few hours later due to its longer half-life.

These new hypnotics also facilitate the easy achievement of good quality sleep, as they do not disrupt its architecture and allow both deep stages III and IV sleep, which is necessary for adequate rest, and REM sleep, which is necessary for dreaming, a process fundamental for the psychological well being.

The side effects are very few but the possibilities of some form of dependence and of synergistic effect with alcohol have not been adequately studied yet. We do not have many studies concerning these issues but the few which exist, give encouraging results.

Most studies, about the use of drugs in military operations, are performed in simulated conditions, which do not fully reproduce the stress of an actual operation (the presence of enemy, loss of companions, unfamiliar and/or hostile environment). Moreover, they do not take into account the pilot's psychological profile and any human weaknesses. Despite the progress of psychopharmacology, chemically induced sleep cannot match the quality of normal sleep and a pilot who needs a drug to get an adequate rest may induce the psychological perception of a dependent person.

Observations from military Air Forces have shown that pilots may occasionally try to confront their stress with alcohol. What could then be the effect of co-administration of a drug and how can the complete absence of a synergistic effect be guarantied? Could the flight surgeon be seen as co-responsible of an accident? Another possibility is that the pilot may, depending on the time and composition of the last meal be at risk of relative hypoglycemia or he may not be at the peak of his health during the operation. What would be the effect of drug administration then?

Also, there should be an urgent operational need, when the drug is near its peak concentration, when the pilot will clearly be unsuitable.

Frequent nocturnal operations disrupt circadian rhythms. In order to deal with this an adequate number of pilots must be required to allow sufficient time for rest and to alternate participation in operations.

Finally, let us not forget that a real combat situation brings to the surface all the aspects of somebody's personality. We are not dealing with a car engine, which regularly needs lubrication for optimum functionality, but with human beings that (may) have ethical dilemmas regarding their mission. Consciences are not determined by propaganda and may revolt particularly when risks of civilian casualties are high. Let us not forget that one of the three Enola-Gay pilots became insane after the bombing of Hiroshima.

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The Effects of Low Frequency Electromagnetic Fields on the Melatonin Synthesis in Man

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Melatonin – synthesis and functions

Some studies (mainly in rodents) have raised concerns regarding a carcinogenic potential of low-frequency electric and/or magnetic fields which may be related to the inhibition of melatonin synthesis. This hormone – isolated by Lerner et al. in 1958 [14] – is thought to exert an oncostatic effect probably by acting as a free radical scavenger [20, 21, 22]. The chronobiological properties of melatonin are much better founded. Melatonin mediates the entrainment (synchronization) of the periodic diurnal alterations of physiologic functions (core temperature, heart rates etc. [2, 4]). Moreover, melatonin has probably numerous other functions which are as yet insufficiently studied (thermoregulation, cardiovascular and immune functions etc.) [6, 7].

Circadian rhythm of melatonin synthesis: Without any time cues, the synthesis of melatonin follows an endogenous circadian rhythm with a period of about 25 hours on the average. The rhythm is controlled by the endogenous pacemaker which is located in the suprachiasmatic nucleus and entrained by the light-dark cycle to a diurnal 24-hours rhythm. The information about the light is transmitted from the retina to the endogenous pacemaker and then via several neurons to the pineal gland, where the synthesis of melatonin is inhibited [3, 12]. The synthesis starts with or after the onset of dark and decreases in the early morning. So, the actual concentration of melatonin reveals a distinct diurnal rhythm.

The onset of melatonin synthesis, the time and the amplitude of its maximum varies considerably between individuals but is rather stable for an individual [1, 3, 8, 9, 26].

Inhibition of melatonin synthesis by electromagnetic waves: Apart from natural light, the synthesis of melatonin is also inhibited by artificial light where the extents of the effects depend on intensity and wavelength as well as on the time and the duration of exposure [2, 10]. Similar, though far smaller effects were evoked in animal experiments by other parts of the electromagnetic spectrum, namely by UV-A radiation (320-400 nm) [5, 19] and by low-frequency magnetic fields [26]. A similar effect may be evoked by thermal radiation as well.

Effects of low-frequency magnetic fields on melatonin synthesis

Animal experiments have unequivocally revealed an inhibititory effect of low-frequency magnetic fields on the synthesis of melatonin. Magnetic fields are presumably perceived as well as light by the photoreceptors of the retina, thus

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suggesting the same underlying mechanism [e.g. 11, 13, 17, 27].

These effects are debated for human beings. Pfluger and Minder [18] observed that railway workers who were exposed during their shifts to magnetic fields (16.7 Hz, 20 μT on the average) excreted less 6-hydroxymelatonin sulfate. But these results are not convincing as the respective workers were also exposed to light during their duties.

Wilson et al. [25] registered a reduced excretion of 6-hydroxymelatonin sulfate in some of their subjects who slept with an electrically heated blanket. Schiffmann et al. [23] observed 8 subjects during a control night without any exposure and during 2 nights with exposure to a magnetic field or to bright light, respectively, between 1 a.m. and 2 a.m.. Actual plasma concentration of melatonin was, however, exclusively reduced after exposure to light.

Selmaoui et al. [24] observed 16 subjects (20-30 yrs) during two 24 h periods. Following a standardized protocol during the day (8 a.m. to 11 p.m.) the subjects were then exposed during the night to a continuous or to an intermittent magnetic field, respectively (50 Hz, 10 μT). Actual plasma concentration of melatonin was determined every hour and the excretion of 6-hydroxymelatonin sulfate over consecutive 3-hour periods. Melatonin production was not influenced compared to a control group comprizing another 16 subjects.

Wood et al. [26] determined a window of temporal sensitivity. In their experiments melatonin synthesis was only suppressed when magnetic fields (50 Hz, 20 μT) were applied before and during the onset of melatonin production in the evening which was determined during a 'baseline night' without any exposure to magnetic fields.

Graham et al. [8, 9] conducted 3 studies, where the subjects were studied first in two control nights to determine the individual basic melatonin production and the individual reaction to light. Basic melatonin production was indicated by a single blood sample taken at 2 a.m. and the effect of light was determined by the difference of plasma concentrations before and after a 1-hour exposure (5 500 lux, 2 a.m to 3 a.m.). During the 3rd night every third subject slept under the influence of an intermittent 60 Hz magnetic field of 2 or 20 μT, respectively or without any exposure (control group). Actual plasma concentration of melatonin was determined every hour. In the first study, subjects with a low level of melatonin revealed a significantly greater inhibition of melatonin synthesis due to light as well as to the stronger magnetic field (20 μT). In both the following studies this result was not replicated. Though carefully executed these 3 studies reveal nevertheless some methodological errors.

- The single determination of melatonin concentration at 2 a.m. does not take into account the considerable differences in the temporal distribution of melatonin synthesis between subjects. Reliable information on basal melatonin production would have required an hourly sampling as it was done in the experimental nights. Thus, the subsequent categorization of an individual's melatonin production is at least questionable.
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- The restriction of the observation period to the duration of sleep and exposure neglects a possible rebound, which would have required an extension of the sampling period [10].
-
- Due to the great differences between subjects a within subject comparison would have been advisable, i.e. sham versus field exposure.

The assumption that individuals react differently to electromagnetic waves (light, magnetic fields) is plausible and the consequences are relevant not only for work. The confirmation of a greater reduction of melatonin synthesis in persons with habitually low melatonin synthesis would imply that particularly babies during the first weeks of life, old people and presumably persons with a late circadian phase (evening types) are affected.

Methods

This study which was started some weeks ago aims to investigate experimentally the effects of extremely low-frequency magnetic fields on the synthesis of melatonin in man. The following requirements are fulfilled:

- within subjects comparisons which presuppose identical procedures during control- and during exposure nights
- frequent (hourly) determination of actual melatonin concentration (saliva)
- observation periods must exceed exposure time to detect rebound effects
- control experiments without any exposure and with exposure to a stimulus with well known effects on melatonin synthesis (light) are advisable.
-

As the actual individual phase might be important, masking effects are avoided by the application of constant routines [15].

Experimental design: The subjects are observed 4 times at weekly intervals for 24-hour periods. Regarding a permuted sequence the exposures listed in the table are planned.

	EMF	Light	Thermal radiation
Control	-	< 50 lux	18 °C
Magnetic field	16.7 Hz, 0.2 mT	< 50 lux	18 °C
Light	-	1 500 lux	18 °C
Thermal radiation	-	< 50 lux	t_r: 65 °C, t_a: 18 °C

The study concerns extremely low-frequency magnetic fields that are emitted by railways (16.7 Hz), to which many persons are regularly and frequently exposed. These are residents living along railway tracks, commuters who are periodically exposed twice a day and the employees of railway companies who are affected during their duties.

Technical equipment: the experiments are executed in 3 rooms, particularly designed and equipped for the respective purpose.
Control experiment and exposure to magnetic fields: The respective observations take place in a sound proofed room with an area of 2.80 m x 3.80 m, where two Helmholtz-coils with a diameter of 1.80 m each are located. The coil-to-coil distance is 92 cm, so that the subjects lie in a horizontally directed homogenuous field. The equipment is particularly designed for low frequency fields.

Thermal radiation: Exposure to thermal radiation takes place in a climatic chamber where radiation temperature (t_r), air temperature (t_a), humidity (RH) and air velocity (v_a), can be varied in a large range and adjusted precisely (t_a: - 35 to + 80 °C, t_r: t_a to + 200 °C, RH: 5 to 99 %, v_a: 0.1 to 4.5 m/s).

Light: Light exposure is realized in another climatic chamber which has the same specifications as the chamber used for radiation exposure. Light can be adjusted up to about 3 000 lux.

Apart from the respective exposure conditions air temperature is adjusted to 18 °C, the irradiance to less than 50 lux and the sound pressure level to 50 dBA (due to air conditioning).

In all these rooms the subjects can get into contact with the experimenter via an intercom system at any time.

Experimental procedure: After their arrival in the institute the subjects assess their actual health state and well-being. They then state their alcohol and drug consumption within the preceding 12 hours. In case of serious disturbances the experiments are postponed to another day.

After the application of the sensors (thermocouples for rectal temperature, electrodes for EKG) the subjects spend 24 hours in bed (noon to noon). Exposure (field, radiation, light) starts at 6 p.m. and is terminated at 2 a.m.. The subjects receive hourly small snacks (200 to 400 kJ). The plate is removed after 30 minutes as the subjects are not allowed to eat during the 30 minutes which preceed the collection of the saliva. So, the experimenters enter the experimental chambers every 30 minutes.

Biochemical, physiological and psychological measurements

Personal characteristics: When the subjects are introduced to the experiments, personal characteristics are determined with the 'Freiburger Personal Inventory'.

Subjective reactions: Immediately after having entered the experimental room and just before leaving the subjects fill in a short questionnaire, where they – using analogue scales – assess their actual mood, tension, tiredness etc..

Actual melatonin concentration: Actual concentration of salivary melatonin are determined hourly.

Actimetry: During observation time body movements are registered using actimeters that are tied to the wrists of the subjects. They allow the reliable detection of body movements, i.e. phases of different physical activity.

Core temperature: Rectal temperature is measured with thermistors (YSI 427 Yellow Springs) continuously 10 cm beyond the sphincter and stored as averages over each consecutive minute.

Heart rates: The electrocardiogram is registered continuously and stored to calculate heart rate variability.

Subjects: Altogether 12-16 healthy male subjects, aged 18 to 30 years are examined. As the individual melatonin synthesis is presumably associated with the individual circadian phase (morning-, evening types), the subjective circadian phase (SCP) [16] is determined with a questionnaire that proved to be a reliable instrument for this purpose.

Exclusion of subjects: Subjects suffering from chronic, particularly from cerebral diseases or having psychic alterations are not allowed to participate. This is verified by questionnaires.

Break-off criteria: The experiments are terminated on request of the subjects. Further break-off criteria are not foreseen.
At present, the data of alltogether 5 subjects are collected, however, not yet evaluated.

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Promoting Sleep: Adapting to Shiftwork and Time Zone Change

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INTRODUCTION

The changes in performance that arise in shiftworkers and after transmeridian flights can be attributed, at least in part, to the reduction in both the quality and quantity of sleep which occurs as a result of disruption of the normal pattern of sleep and wakefulness. Sleep disturbance associated with shiftwork is well documented (1-4). Sleep during the day is shorter and more disturbed than sleep at night, and it has been estimated that, by the end of a week of night duty, the equivalent of at least one night's sleep may have been lost (5). While the duration of slow-wave sleep is unchanged following the night shift, due to prior wakefulness, stage 2 and rapid eye movement (REM) sleep are reduced. Further, in shiftworkers over about 40 years old, the usual decline in sleep quality and quantity with increasing age exacerbates the problems associated with an unusual pattern of work and rest (6-8). This age-related difference in sleep is also evident in studies of transmeridian travel (9).

There have been many studies of sleep after transmeridian flights. In general, the severity of sleep disturbance following a time zone change is dependent upon the direction of travel and the number of time zones crossed, and is influenced by the timing of the flight itself (10-12). After an eastward journey, when sleep is scheduled in advance of the "home" bedtime, difficulty in falling asleep may be accompanied by increased wakefulness in the early part of the night, though these changes may not be apparent on the first night in the new time zone if the flight involves overnight travel without sleep. Problems with sleep may continue for several days after the flight, with reductions in REM sleep and possibly slow-wave sleep, and this may be followed by a compensatory increase in REM sleep several nights later. Sleep disturbance after a westward flight is usually less persistent, lasting perhaps 2 or 3 days. Sleep is likely to be of good quality in the early part of the night, with increased slow-wave activity on the first night due to the delay to the first rest period. On subsequent nights, when the pressure for slow-wave sleep is less, there may be an increase in REM sleep as bedtime corresponds with early morning in the "home" time zone, when REM sleep predominates and body temperature begins to rise (13,14). Awakenings may be evident towards the end of the night at the time corresponding to daytime in the "home" time zone.

Given the adverse effects of sleep loss on alertness, one approach to optimizing performance in situations involving shiftwork or transmeridian flights is to preserve sleep as much as possible. This can be approached in two ways: first, by the application of sleep-promoting techniques and by attention to the circumstances which surround sleep; and second by the use of hypnotic substances. Sleep may, of course, be improved by changing duty schedules or resetting the body clock, but these techniques are outside the scope of this paper.

Paper presented at the RTO HFM Workshop on "Individual Differences in the Adaptability to Irregular Rest-Work Rhythms/Status of the Use of Drugs in Sleep-Wakefulness Management", held in Venice, Italy, 3-4 June 1999, and published in RTO MP-31.

TECHNIQUES TO IMPROVE SLEEP

Among the techniques or strategies that may be applied to promote sleep are those which aim to ensure that the sleeping environment is optimal. While it is true that shiftworkers sleep badly even in sound- and light-proofed accommodation (15), sleep will be more disturbed if the environment is noisy and light. Similarly, after transmeridian flight, it is important to ensure that extraneous noise and light are kept to a minimum to alleviate problems related to staying asleep in the morning or to falling asleep at night. If the sleeping environment is not ideal, earplugs and eyeshades can be used to screen unwanted external stimuli. These strategies are frequently used by airline pilots sleeping in hotel accommodation or when they have to obtain rest in the bunk facilities on board the aircraft itself on long-range flights (9). Aromatherapy products have also been promoted for the treatment of jet lag and sleep disturbance.

Caffeine (Fig 1) and alcohol are known to have detrimental effects on sleep (16,17) though alcohol may initially promote sleep onset. Avoidance of caffeine close to bedtime and of excessive alcohol intake are measures that will serve to improve the sleep of shiftworkers and intercontinental travellers. The influence of dietary constituents has also been considered, and it has been suggested that a "jet lag diet" will speed adaptation of sleep and other rhythms (18). This diet proposes that an evening meal rich in carbohydrates will provide a source of tryptophan for serotonin synthesis to assist sleep, and that protein-rich meals in the morning will provide tyrosine to enhance catecholamine levels and increase alertness during the day. However, a review of this field of research concluded that there was no evidence to support this approach (19). Administration of tryptophan has been reported to increase total sleep time on the first night after transmeridian travel westward (20), though its effects on sleep are limited (21)

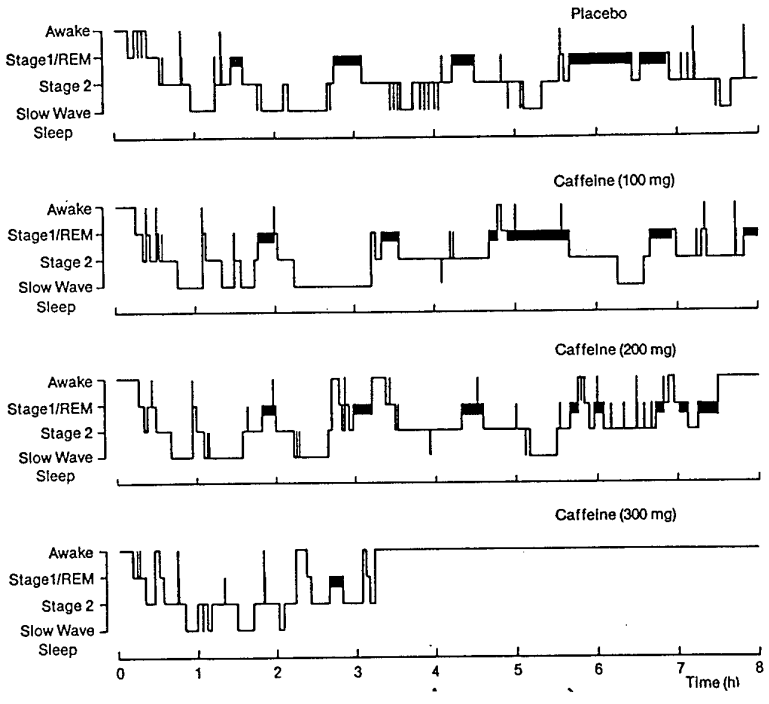

Fig 1 Effect of caffeine (100, 200 & 300mg) on sleep in a normal subject.

Changes in the timing of rest periods and naps during shiftwork or after a time zone change can lead to improvements in sleep. However, it is necessary to balance the changeover times of shifts as sleep duration is reduced if the morning shift starts early or if the night shift finishes late (22). During transmeridian travel, if it is not possible to sleep during an overnight eastward flight, restricting sleep on arrival can aid sleep on the first night and, possibly, speed the rate of adaptation. If passengers are able to sleep on board the aircraft, then sleep coinciding with bedtime in the destination time zone will avoid the desire for a sleep on arrival and is likely to lead to better-quality nocturnal sleep. Conversely, sleeping at a time coinciding with night-time in the home time zone may lead to disturbed sleep at the destination and, possibly, delayed adaptation.

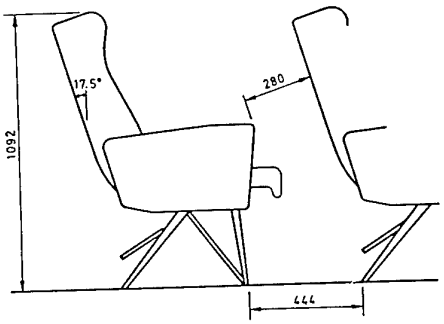

Fig 2 Armchair. The back angle with the verticale is 17.5°. but there is no rest for the legs or feet.

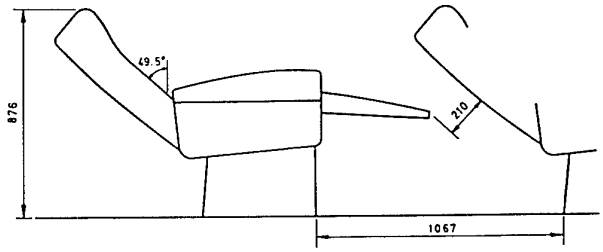

Fig 3 Sleeperette. The back angle with the vertical is 49.5°, and the rest provides horizontal support for the legs.

Finally, sleeping position is also important, and particularly relevant to long-haul air travel (Figs 2, 3 & 4). Passengers on board aircraft are required to adopt a posture that may make sleeping difficult. Near-horizontal sleeping facilities are preferable, but they are at present limited. Assessment of sleep quality in aircraft seats has shown that the greater the back angle from the vertical, the more likely it is that the passenger will obtain reasonable sleep. Adequate sleep is likely as long as the back angle is around 40 degrees (23). Over the last few years there have been many improvements including full sleeping facilities.

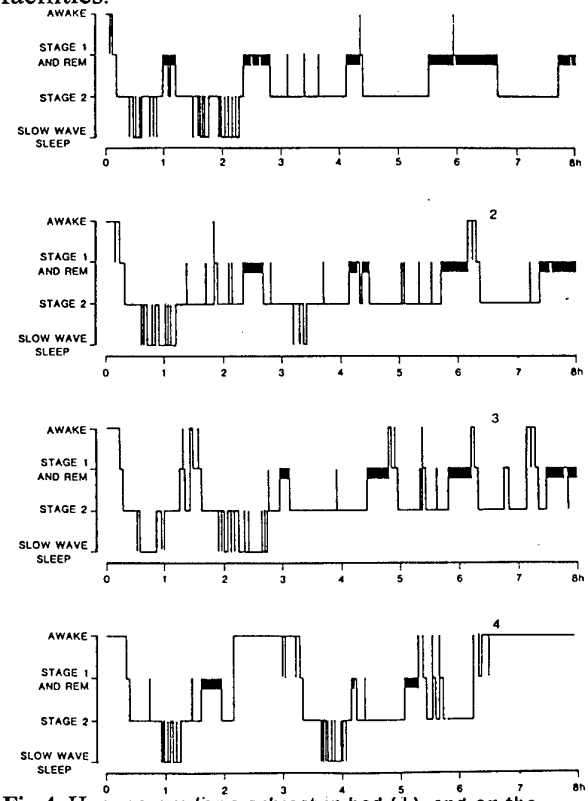

Fig 4 Hypnogram for a subject in bed (1), and on the sleeperette (2), reclining seat (3) and armchair (4). Sleep was markedly disturbed in the armchair with an hour period of wakefulness, and shortened sleep. Sleep in the reclining seat also showed some disturbance, with more awakenings particularly during the latter part of the night.

HYPNOTIC DRUGS AND SLEEP-PROMOTING SUBSTANCES

The second approach to preserving sleep involves the use of drugs. The largest class of hypnotics, the benzodiazepines, is known to speed sleep onset, reduce awakenings, and increase total sleep time in normal sleepers and in those suffering from transient and chronic insomnia. However, they may delay the appearance of REM sleep, reduce slow-wave sleep, and enhance sleep spindles (24-27). Imidazopyridine, zolpidem, and the cyclopyrrolone, zopiclone, have similar effects on the EEG as benzodiazepines (28,29). Zolpidem, however, may increase slow-wave sleep (Fig 5), at least in young individuals (29,30), and there may be a moderate increase in slow-wave sleep with zopiclone (31).

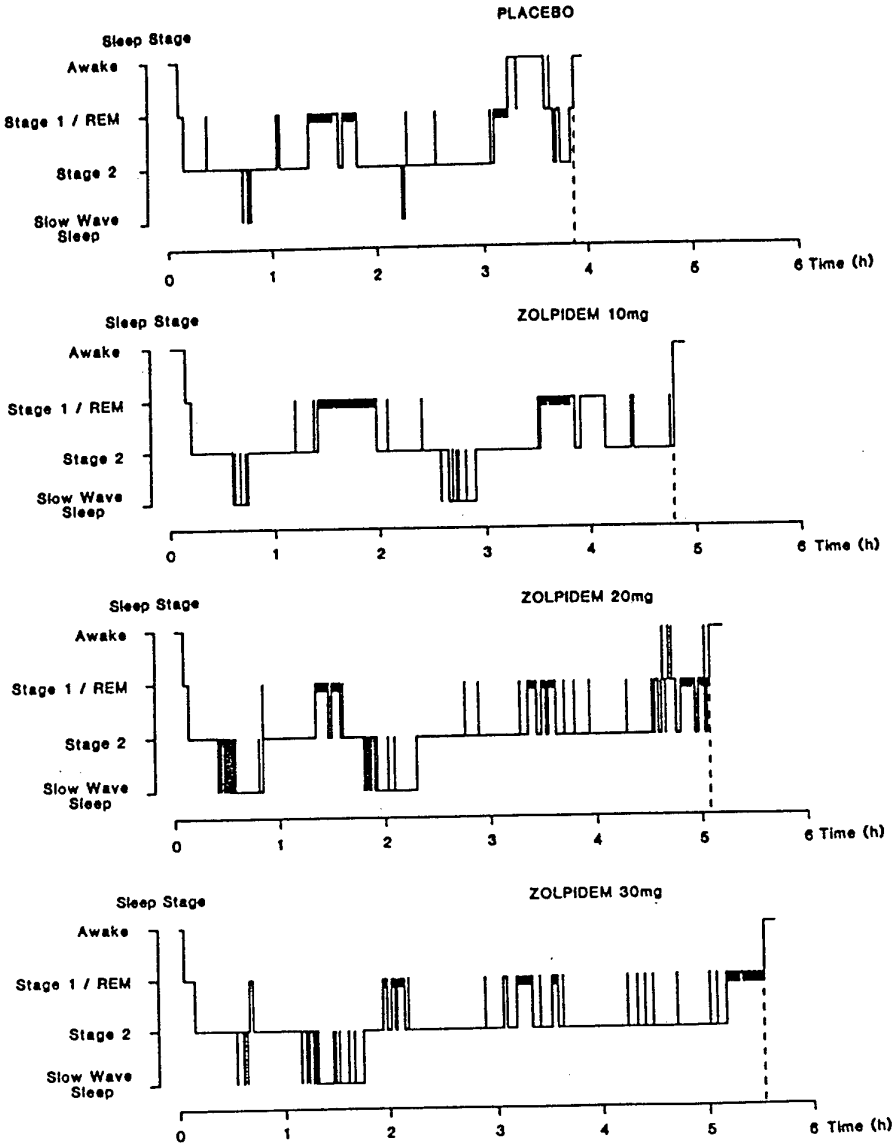

Fig 5 Daytime sleep patterns of a young adult after ingestion of placebo and 10, 20 and 30mg zolpidem. Wakefulness was reduced with zolpidem and sleep period time was increased. With 20 and 30mg there was an increase in the duration of slow wave sleep and total sleep time.

While a hypnotic should, ideally, accelerate sleep onset and sustain sleep for a useful period of time, and while it may be desirable to preserve slow-wave sleep, the overriding factor when considering the potential use of a hypnotic by shiftworkers or during and/or after transmeridian flights is the drug's duration of action (32). Active metabolites may also prolong the duration of action of a particular drug. Clearly, the benefits associated with improved sleep may well be offset if the hypnotic leads to unwanted effects on alertness after the rest period. An hypnotic that is rapidly cleared and is without active metabolites, is likely to be free of residual effects and without accumulation if taken daily. However, it must be appreciated that clearance is dependent on absorption, distribution and elimination, and all these factors must be taken into consideration when duration of action is being determined. Drugs with appropriate pharmacokinetic profiles have been evaluated in simulated and field studies of shiftwork and jet lag. In such situations, hypnotics are likely to be effective due to their sleep-promoting properties rather than any effect on circadian rhythms.

TRANSMERIDIAN TRAVEL

Hypnotics with a limited duration of action may be useful during the adaptation phase after a transmeridian flight. For example, temazepam taken during eastward and westward flights across 11 time zones at the time corresponding to bedtime in the destination time zone and for 4 days after arrival improved subjectively assessed sleep without affecting performance during the day (33). In another study brotizolam reduced wakefulness and increased stage 2 sleep on the first 2 nights after a 5h westward time zone change (Fig 6) and the drug was also effective in reducing wakefulness and stage 1 sleep for 5 nights after the eastward journey (10) (Fig 7). Improvements in sleep continuity with hypnotics several days after an eastward flight may be accompanied by a reduction in REM sleep on those nights when an increase is observed with placebo (12).

However, the effects depend on the extent of sleep disturbance, which, in turn, depends on the direction of travel, number of time zones crossed, and the age of the individual. For example, the short-acting hypnotic midazolam, taken for 4 nights after a 7h time zone change, improved sleep, though only after the eastward flight on the first and third night when sleep with placebo was poor (34). Similarly, on the first night after an eastward flight when sleep after placebo was better than control due to considerable sleep loss, it was not possible to show a further improvement in sleep with brotizolam (10).

In addition to using hypnotic drugs on arrival in a new time zone, passengers may consider using medication on the flight itself to assist sleep timed to coincide with the nocturnal rest period at their destination. In an unfavourable environment simulating troop transportation, the hypnotics triazolam and zolpidem, with elimination half lives of between 1.5 and 2h, had comparable sleep-promoting properties (35). However, a field study suggested that triazolam may be ineffective on board an aircraft if there is no control over factors such as the timing of meals or the cabin lighting (36). Indeed, to sustain sleep during a long flight, a hypnotic with less rapid clearance may be more appropriate.

In a laboratory study of sleep in airline seats, though midazolam and brotizolam improved sleep, midazolam further suppressed REM sleep to below levels that were already reduced by sleeping in the seat (37). An additional consideration of taking a high dose of a rapidly eliminated hypnotic is the possibility that high plasma levels may impair performance in an emergency situation (35) or on arrival at the destination

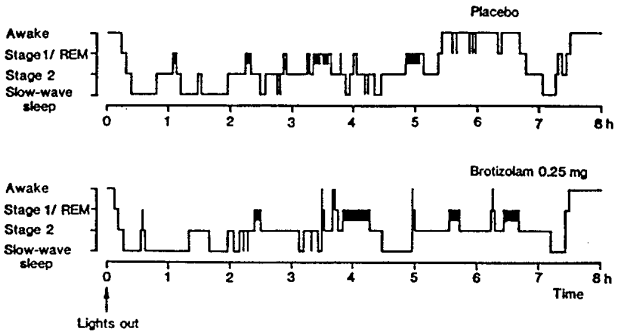

Fig 6 Sleep patterns of an individual on the first night after a 5h westward time zone change after placebo and brotizolam ingestion at lights out (13).

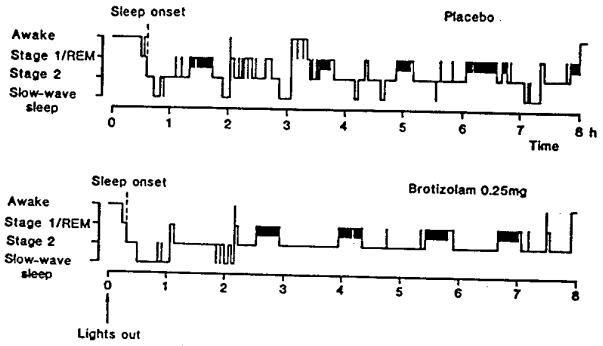

Fig 7 Sleep patterns of an individual on the fourth night after a 5h eastward time zone change after placebo and brotizolam ingestion at lights out (13).

(36), and there could be rebound effects on sleep parameters during the next rest period.

Melatonin has been reported to improve the subjective adverse effects of jet lag in a number of studies (38-42), though some of these studies have shown no effect on measures of sleep duration. In one study of military personnel following an 8 hour eastward time zone shift 10mg melatonin was reported to advance the timing of sleep and increase sleep duration measured by actigraphy (42). There have, however, been reports of sleep difficulties after melatonin (5mg) use in the treatment of jet lag (41). Sleep fragmentation with melatonin (5mg) has also been observed in laboratory studies (43). The only sleep EEG data relates to laboratory studies of simulated change using 5mg melatonin. This showed some increases in sleep duration and efficiency in the first night after the phase shift, but also reductions in slow wave sleep (44).

SHIFTWORK

Hypnotics may also be used by shiftworkers, and a recent review (45) concluded that hypnotics improve daytime sleep by increasing sleep efficiency and duration. Interestingly, the efficacy of hypnotics for nocturnal sleep may not always predict their effectiveness for daytime sleep. With this in mind, evaluation of new compounds should include assessment of sleep-promoting properties at the relevant times of the day. Such studies would also take account of the further, different sleep problems experienced by shiftworkers in relation to their different schedules. As far as the night shiftworker is concerned, sleep onset is not likely to be as much of a problem as sustaining sleep during the day, whereas those working an early-morning shift who choose to retire to bed in the early evening may have difficulty falling asleep.

To date, the majority of studies on hypnotics and shiftwork have been laboratory-based simulations. In these situations the effects of cumulative sleep loss may be underestimated when using subjects who are not shiftworkers, particularly if they are young adults who are normally good sleepers. In addition, sleep is more likely to

be sustained when environmental conditions are controlled. For example, triazolam was more effective in sustaining daytime sleep in middle-aged shiftworkers who slept in the laboratory (46) than in middle-aged individuals who slept at home (47).

Studies suggest that the less restful sleep of the middle-aged is more likely to be improved by hypnotics than the sleep of young adults (30,48), and older shiftworkers have reported greater use of sleeping pills than their younger colleagues (8,49). Furthermore, it is possible that middle-aged individuals may derive greater benefit from hypnotics in terms of improved alertness overnight (47,48) than young adults. Indeed, for young subjects who are good sleepers there may be no difference in overnight performance following a drug-assisted or natural evening sleep (50).

Another factor to consider is the potential effects of withdrawal of medication. Withdrawal of triazolam after 4 days for daytime sleep led to a greater reduction in sleep efficiency in middle aged individuals than young adults (48), though the rebound effects may have been related to the high dose used (0.5mg). Indeed, this dose of trazolam has been shown to impair performance following daytime sleep (46), overnight sleep (51), and both sleep on board aircraft (37) and in conditions simulating those on board aircraft (36). While a lower dose of triazolam (0.25mg) has been shown to improve subjectively assessed sleep without having residual sequelae in military shiftworkers with disturbed sleep (52), other studies suggest that low doses of hypnotics may not be effective in some middle-aged individuals (47,53,54).

It is important to balance the requirement to improve sleep with the need to avoid residual effects. Zolpidem has a pharmacokinetic profile similar to triazolam (32) and, though it would appear to be free of residual effects, improvements in daytime sleep were only observed at relatively high doses (20-30mg) in young adults and were accompanied by a reduction in REM sleep (30). While zolpidem may be more effective in poor sleepers a sufficiently long duration of action is important in sustaining daytime sleep. For example, temazepam has been used successfully in doses of 10-20mg by military aircrew to assist sleep at unusual times of the day during intensive operations when the interval between drug ingestion and commencement of duty may be as short as 6h (55,56). Similarly, temazepam improved daytime sleep and increased alertness during a simulated night shift (57). Zopiclone may be an equally effective hypnotic as it improved sleep when bedtime was advanced by 4h (58) and when advanced or delayed by 6h (59). Decrements in performance some 9h after drug ingestion have been reported (35), and a recent review of its residual effects has indicated caution in its use in critical situations (60).

There have been two field studies which have investigated the use of melatonin to assist adaptation to shiftwork, though only one of these monitored sleep (61,62). A 5mg dose prior to daytime sleep during a period of 7 consecutive night shifts was reported to improve sleep quality and quantity assessed subjectively. In a study simulating night shiftwork, melatonin was reported to improve daytime sleep quality as measured by actigraphy (63).

CONCLUSION

In summary, management of sleep disturbance arising from shiftwork and transmeridian travel should be approached by attention to sleep hygiene, including

factors such as sleep timing, environmental conditions, and restriction of "social" drugs. However, the successful application of such measures is not well documented. If such an approach is ineffective and due attention has been given to optimizing duty schedules then the occasional use of an hypnotic free from residual effects and of accumulation on daily ingestion may be indicated. The lowest effective dose should be used and the concomitant use of alcohol avoided or restricted.

Studies reporting beneficial effects of melatonin in the treatment of jet lag have largely been based on subjective assessments, with only two studies monitoring physiological rhythms. There is some evidence from laboratory investigations that melatonin does have circadian phase shifting properties, but there is litte or no information available on the effect of melatonin upon objective measures of performance and sleep in the field. In the laboratory the observed effects of melatonin on sleep have been inconsistent.

Advice on the use of hypnotics requires further clarification, particularly for those individuals with poor sleep who frequently undertake night shiftwork or regularly cross time zones. The potential users should be aware of the general recommendation that hypnotics should only be taken occasionally. For example, this could involve using a suitable hypnotic on alternate days at the start of a period of nightwork, so that a sleep deficit does not accumulate. Dissemination of current knowledge and guidelines on promoting sleep to occupational physicians, shiftworkers, and transmeridian travellers should be encouraged. At present, however, there is little information on the pattern of hypnotic usage and efficacy in shiftworkers over time. Further research in this area, including feedback from users, would allow better definition of the most suitable treatments.

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CAFFEINE TO SUSTAIN OPERATIONAL FATIGUE

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Sleep deprivation and desynchronization from circadian rhythm are common in military operation. Caffeine is the most widely used psychostimulant and may be useful in operational fatigue-coping strategies. In this paper we will review the current policies on caffeine in the military, then we will discuss effects and potential use of a slow release caffeine formulation.

1. Current caffeine use in the military.

1.1. Pharmacology.

Caffeine is a naturally occurring xanthine derivative (table I). Metabolism is virtually confined to the liver. Caffeine half life is prolonged in pregnancy and with oral contraceptives, and is shortened in smokers and heavy caffeine users. Its stimulant effect is connected to the blocking of A_1 adenosine receptors. Caffeinism syndrome is observed with too much caffeine consumption. Symptoms are : restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal (GI) complaints, muscle twitching, palpitation, psychomotor agitation. Caffeine withdrawal may cause headache, fatigue, anxiety, insomnia, nausea, performance impairments. Symptoms are observed between 12 hours and 1 week after the last caffeine intake, with a peak intensity at 48 hours.

Table I: Caffeine dietary sources	
coffee	60-120 mg/cup
Tea	40-60 mg/cup
Hot chocolate	20 mg/cup
Soft drinks	40 mg/360 ml serving
Chocolate bar	20 mg/bar

1.2. Caffeine in the USAF.

In the USAF in 1995 (1), caffeine was recommended as a stimulant for enhancing vigilance, alertness, mood or to delay sleep. Flight surgeons had to be aware of its diuretic effect that may increase dehydration on prolonged flights. Caffeine intake was to be avoided within 6 hours of bed time and the tablet form was not authorized.

1.3. Caffeine in the US Navy.

A survey conducted aboard USS America during Desert Shield and Desert Storm operations over Iraq showed different patterns of caffeine use. In the attack community A-6 aviators used to drink 2 cups per day, whereas F-14 aircrew drunk 3-4 cups per day. Most caffeine was ingested on non flying days during Desert Shield and on days with flight during Desert Storm. Shorter nap duration was associated with greater caffeine use (2).

Another survey was done on USS Independence in 1992 during Operation Southern Watch over Iraq (3). It provided data about the most commonly used performance maintenance modalities in aircrew during 18 days of intensive carrier operation (table II). Coffee and caffeine tablets were the most consumed stimulants.

Currently in the US Navy, caffeine is the only approved chemical for use to promote alertness in prolonged operations. No limits on caffeine intake are set, but aircrew are grounded if they present any side effects.

Table II: commonly use performance maintenance modalities (US Navy, Belland & Bissel,1994).	
modality	*number*
none	44
coffee	39, average 1-2 cups before flying
caffeine tablets (75 mg)	18
no response	05
candy	05
soda	04
snuff tobacco	03
iced tea	03
nicotine gum	02
tobacco cigarettes	02

1.4. Caffeine in the French military.

Coffee is not restricted for French aircrew, and caffeine tablets are not approved.

2. Slow Release Caffeine (SRC).

2.1. Pharmacokinetics.

This SRC formulation increases the mean delay to peak plasma concentration (C_{max}) and lowers the C_{max} (table III). We evaluated the effects of SRC in 2 sleep deprivation experiments.

Table III: caffeine/SRC pharmacokinetics				
Caffeine 300 mg/60kg	C_{max} µg/ml plasma	T_{max} h	$T_{½}$ h	AUC µg/ml plasma. h
Aqueous solution	6.9 ± 0.3	1.2 ± 0.2	5.4 ± 0.6	57.8 ± 4.9
Slow release	5.5 ± 0.3	4.1 ± 0.3	5.1 ± 0.6	54.2 ± 6.4

2.2. 34-hour sleep deprivation.

2.2.1. Protocol.

In this double blind, placebo (PBO) controlled, cross over study, we evaluated SRC 300 mg in 24 sleep deprived young healthy subjects (4). The 12 females (using oral contraceptives) and 12 males volunteers

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(mean age 24 years) came at the laboratory at 06:00h, on day 1 (D1) and were maintained awake until the end of the session on D2 at 17:30h. They took the treatment (PBO or SRC 300 mg) at time zero (H0), which took place between 00:00h and 01:30h. Alertness, mood, subjective sleep and performance were assessed during 2-hour session tests at H2, H9 and H13, with a 34 h maximum sleep deprivation. The tests included : blood pressure and heart rate monitoring, psychomotor tests, Standardized Test for Research with Environmental Stressors (STRES) battery (6), Multiple Sleep Latency Test (MSLT), focused attentional test (BATP), mood, alertness and sleep evaluation by visual analogue scales (VAS). Circulating caffeine levels were assessed in salivary samples.

2.2.2. Results.

With PBO, nausea and vomiting occured in 2 females volunteers. With SRC one male subjects complained of mild GI disorders and 4 female subjects reported mild tremor, nausea or palpitation.

Cardiovascular parameters were not influenced by treatment. Caffeine in women had a salivary peak concentration and bioavailability (AUC) higher than men : $C_{max\ salivary}$ = 4.7 µg/ml (female) versus 2.4 µg/ml (male), AUC = 77.6 µg/ml.h (female) versus 30.6 µg/ml.h (male). Caffeine half life (T ½) was longer in the female group : T ½ = 7.6 h (female) versus 4.8 h (male).

Sleep latency, evaluated by MSLT, was significantly longer with SRC (table IV). Most of performance improvements (STRES battery) occured at H9 for men and H9 and H13 for women. With PBO, female and male subjects reported similar scores for calmness and contentedness (Bond and Lader VAS) (5), whereas a decrease in alertness appeared in the female group. In both sexes, alertness was enhanced by SRC. During the recovery night, mean sleep duration, sleep onset latency and quality of sleep were not influenced by treatment.

Table IV: MSLT in minutes and seconds

Time H 0 = drug intake	PBO mean ± sem	SRC 300 mg mean ± sem
H 2.5	6:05 ± 1:50	11:40 ± 1:02
H 9.5	3:22 ± 0:45	4:40 ± 0:18
H 13.5	2:50 ± 0:49	4:30 ± 0.39

2.2.3. Discussion.

In this 34-hour sleep deprivation experiment, SRC action is extended in female subjects, who exhibited also more adverse events with both treatments, than their male colleagues. This sex effect may be explained by the higher sensitivity to sleep deprivation and higher circulating caffeine levels observed in female volunteers, who used oral contraceptives, known to prolong caffeine half life.

2.3. 64 hour-sleep deprivation.

2.3.1. Protocol.

In this double blind, placebo controlled, cross over study, 16 young healthy male volunteers were exposed to a 64 h sleep deprivation period, to evaluate the effects of SRC 300 mg (7). Subjects took SRC every 12 h, from D1 21:00h to D3 09:00h. Test sessions included: BATP and STRES battery and were performed 4 times per 24 h at 10:00h, 14:00h, 21:00h, 02:00h. During the recovery period (2 nights), sleep was limited to 8 h per night and subjects were tested only during the day: sessions R1 and R2 on D4 and R3 and R4 on D5.

2.3.2. Results.

Attentional performance (BATP) was better with caffeine than with PBO from 15 to 55 hours of sleep deprivation. Both treatments showed a sharp performance change after 41h (figure1). During

Figure 1: BATP, %

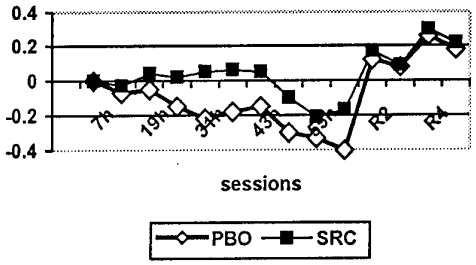


Figure 2: SPATIAL, error %

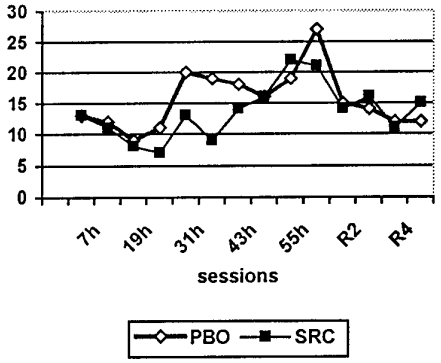
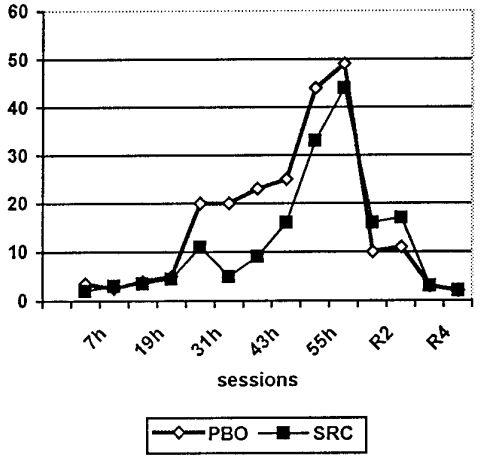


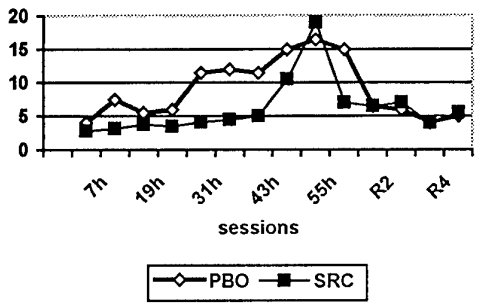
Figure 3: TRACKING, lost controls



recovery period, no difference was observed between treatment.

Performance of subjects was better with SRC whatever the STRES battery task (reaction time, mathematical, memory, spatial, tracking, dual tasks) up to 45 h of sleep deprivation (figures 2, 3, 4).

Figure 4: DOUBLE TASK memory/4 letters, error %



Conclusions.

Modern warfare exposes military personnel to sleep deprivation and desynchronization, while their tasks are more cognitively demanding. To maintain performance in such conditions, aircrew often rely on natural stimulants. Coffee is the most widely used and its acceptance, tolerance and side effects are well known. The development of a new slow-release caffeine formulation may optimize the caffeine consumption strategy in an operational environment. Due to its pharmacokinetic properties, SRC 300 mg is effective to maintain cognitive performance during limited (45 h) sleep deprivation. However, like an aqueous caffeine solution (coffee), SRC is not immune of adverse effects. Therefore SRC should be individually tested prior to operational use. Female subjects using oral contraceptives are more likely to express side effects.

Potential use also concerns desynchronization from physiological rhythm (jet-lag, night duty). A major experiment, Pegasus Operation, directed by Drs D. Lagarde and J. French, from IMASSA, Fr, and Brooks AFB, US, will address that issue. This study, completed in 1998, and involving 27 US military personnel flown from Texas to France, evaluated the use of SRC 300 mg, taken daily for 5 days, as a counter-measure to jet-lag.

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The Effects of Tyrosine on Cognitive Functions during Sustained Operations

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Abstract

The effect of supplementation of the amino acid L-tyrosine on cognitive task performance was assessed during a highly demanding two-week combat training course. A tyrosine group (10 subjects) received daily doses of a protein-rich drink (containing 2 g tyrosine), while a placebo group (11 subjects) received the same doses of a carbohydrate rich drink (containing no proteins). Cognitive task performance was evaluated immediately preceding the course, as well as at the end of the first week of the course. Although there were no group differences in task performance prior to the course, the tyrosine group clearly performed better than the placebo group on several cognitive performance tasks during the course. Overall, up to 40% of the cognitive performance decrement that was due to the impact of stress and fatigue, was counteracted by the supplementation of tyrosine. The findings suggest that tyrosine supplementation can be effective in preventing cognitive degradation in highly demanding military operational environments that include sustained operations, as well as physical and psychological stressors.

Introduction

It is a well documented fact that the psychological stress, as well as the fatigue that are implicated in sustained operations, may affect various aspects of cognitive functioning[1, 2]. This may cause a deterioration of the performance of information-processing and psychomotor tasks, which may, in turn, reduce operational effectiveness and compromise safety. A wide variety of measures have been employed to counteract the cognitive degradation, including stimulating and depressing drugs, as well as resource management, sleep and work/rest management, and physical fitness training. The present study focuses on a relatively new approach: the prevention of cognitive performance degradation through supplementary nutrition. The approach is based on observation that the amino acid L-tyrosine, which is a precursor of norepinephrine (NE), may enhance NE synthesis in the brain[3], and may thus prevent stress- and fatigue-induced NE depletion.

As has been well established, during exposure to stressful conditions, there is an increase in the release of peripheral as well as brain NE[4,5], and it has been shown that the transmission of nor-adrenergic neurons is increased during stress[3, 6]. Noradrenergic projections from the locus coeruleus, providing the main innervation to the frontal cortex and demonstrating increased electrical activity during stress [7, 8], play an important role in attention, alertness, motor activity and the regulation of emotional processes[9]. Accordingly, it has been found that the depletion of brain NE that results from the enhanced release during exposure to stressful conditions, may have a negative behavioral and cognitive impact. NE depletion has been observed to reduce explorative behavior and motor activity, and to induce behavioral depression in animals[10, 11]. In humans, clonidine-induced inhibition of NE release resulted in an increase in the number of lapses of attention, which could be reversed by the antagonist idazoxan[12].

Conversely, there is suggestive evidence that the detrimental effects of NE depletion may be counteracted by administration of tyrosine. In rats receiving a tyrosine-rich diet, neither NE depletion nor behavioral impairments were found after stress industion[10, 13]. In humans, similar results were obtained. Supplementation of 100 mg/kg tyrosine caused a reduction of the number psychomotor impairments and stress symptoms during exposure to cold and hypoxia, compared to a placebo[14]. Similarly, administration of 150 mg/kg tyrosine prevented the cold-induced impairment of short-term memory that was observed in a placebo group[15]. Furthermore, cognitive task performance during exposure to 90 dB noise was found to be superior in a group of subjects that was supplemented with 100 mg/kg tyrosine than in a placebo group[16]. The available evidence, therefore, strongly suggests that supplementation with tyrosine may serve to reduce the detrimental cognitive and behavioral effects of exposure to stress.

The feasibility of dietary tyrosine supplementation is suggested by the fact that protein-containing diets have been found to increase the plasma tyrosine/large neutral amino acids (LNAA) ratio and brain tyrosine levels. Plasma tyrosine concentration, expressed relative to the plasma concentrations of the same transport competitive

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amino acid (tyrosine/LNAA) reflects the amount of tyrosine available to the brain for catecholamine synthesis. In rats, the acute consumption of a high-protein meal has been observed to almost double the serum tyrosine level and the tyrosine/LNAA ratio[17, 18]. In humans, plasma tyrosine levels and the plasma tyrosine ratio were shown to increase significantly when a protein-rich diet was consumed[19]. In another study, oral protein (albumin) was found to increase the plasma tyrosine/LNAA ratio in healthy fasting females by 20-60%[20]. Finally, a protein-rich breakfast was found to cause a significant increase in cerebrospinal fluid tyrosine in patients suffering from normal pressure hydrocephalus[21].

The aim of the present study was to assess whether supplementation of L-tyrosine would be effective in reducing the effects of stress and fatigue on cognitive functioning during sustained military operations. In addition to cognitive task performance, mood states were evaluated, in order to assess whether the tyrosine supplementation would also reduce the subjective effects of stress and fatigue.

The study was carried out among a group of cadets from the Netherlands Royal Military Academy who had to complete a combat training course (CTC) as part of their training program. The CTC encompassed a range of psychologically, as well as physically highly demanding conditions, including sustained operations and sleep loss.

Method

Subjects

Thirty-two cadets of the Royal Military Academy (Koninklijke Militaire Academie; KMA) volunteered to participate in the study. Sixteen subjects (Ss) were randomly assigned to a tyrosine group, and the remaining sixteen Ss were assigned to a placebo group. In the course of the CTC, eleven Ss dropped out due to injuries, etc., leaving a total of twenty-one Ss for analysis (tyrosine group: ten Ss; placebo group: eleven Ss). The tyrosine group included one female and 9 males aged between 19 and 26 years, with a mean age of (± SD) 22.8 (± 2.7). The placebo group consisted only of males, aged between 18 and 27 years, with a mean age of (± SD) 21.4 (± 2.8) years.

Each participant received $ 30.00 at the end of the study. The study protocol was approved by the Medical Ethical Committee of the Free University Hospital, and all Ss gave their written consent to participate.

Apparatus

Cognitive performance tasks. The cognitive performance tasks were presented via eight PC systems, equipped with a timer/response card (TNO), an A/D conversion card (Data Translation DT 2808), a response panel and a joystick. Four tasks from the Taskomat Battery[22] were employed: (1) a memory comparison task (MCT), (2) a tracking task (TT), (3) a continuous memory task (CMT), and (4) a double task (DT).

The MCT evaluates the speed and accuracy of short-term memory comparisons. During the MCT, stimulus trials (an arrangement of 1, 2 or 4 letters), were presented successively on the computer display. The Ss were required to monitor the stimuli for the occurrence of one out of four prespecified target letters, and to respond as fast as possible by pressing a "yes" button if a target letter was present, or a "no" button if this was not the case. After an incorrect response, the word "incorrect" was displayed. The interval between the response and the next trial was 500 ms. If a 1,000 ms deadline had elapsed without a response, the next trial was presented and a response omission recorded. The duration of the MCT was 8 min. The performance measures were the number of correct and incorrect responses.

The TT evaluates perceptual-motor skills. During the TT, a track moved upward in a variable direction on the display. The Ss had to horizontally move a gateway using the joystick, in order to keep the track in the middle of the gateway. The Ss could anticipate the direction of the movements of the track with a 'preview time' of 2,300 ms. The duration of the TT presentation was 7 min. (14 intervals of 30 sec.). The performance measure was the root mean square (RMS) of the distance between the track and the middle of the gateway. This measure was computed separately for each 30 s interval, as well as for the entire task period.

The CMT evaluates the accuracy of short-term memory rehearsal. During the CMT, stimulus trials containing arrangements of 1,2 or 4 letters were successively presented on the display. As was the case in the MCT, the Ss were required to press a 'yes' button when one out of four prespecified target letters was present (no 'no' button was employed in this task). In contrast with the MCT however, the Ss had to additionally count the number of times each of the four target letters was presented in the 7-min. task period, and to type in these numbers on the keyboard after completion of the task. Performance measures were the number of correct responses, and the number of incorrect counts.

During the DT, the TT and the CMT were presented simultaneously. The DT was presented for 7 min (14 intervals of 30 s each). The performance measures included the TT, as well as the CMT performance.

During the performance of the tasks, the Ss frequently suffered from lapses of attention, resulting in temporary interruptions in the execution of the tasks. In the TT (as well as in the DT), this caused them to occasionally leave the joystick in a fixed position. As a consequence, the variability of the RMS values in these tasks was not always associated with real variability in the task performance, but rather with variations in the distance of the track with respect to the (fixed) gateway. Hence, the RMS did not always accurately reflect task performance. This prob-

lem was resolved by employing another performance measure: task-interruption time (TIT). The TIT reflects the percentage of time on task the joystick was not moved. TIT was determined for each subject by counting the number of 30-s periods that the RMS exceeded a cut-off value of 50. The choice of this cut-off value was based on the observation that a failure to move the joystick almost invariably yields mean RMS values > 50[23].

Mood questionnaire. The Profile of Mood States (POMS) is a questionnaire that is designed to evaluate mood states[24, 25] that includes the following subscales: Depression, Anger, Fatigue, Vigor and Tension. In this study, the shortened Dutch version of the POMS was employed[26]. Responses are made by choosing from five response alternatives.

Procedure

Prior to the study, all cadets participating in the CTC had been had been informed about the goal and procedure of the study. Following this, volunteers were invited to participate in the study.

Two weeks prior to the commencement of the CTC, all Ss practised the cognitive performance tasks. The practice session, during which shortened versions of all tasks were presented, was held in a classroom of the KMA. At the end of the practice session, the mood questionnaire was distributed and instructions were given concerning its completion. The Ss were requested to send the completed questionnaires to the second author, using a stamped and addressed envelope, before the start of the training course.

The pre-test session, which was also held in a classroom of the KMA, took place one week prior to the CTC. The pre-test session had a duration of 45 min. The cognitive performance tests were presented in the following order: MCT (8 min), TT (7 min), CMT (7 min), and DT (7 min). In addition to the computer tests, blood pressure was determined, urine samples were taken, and a mood questionnaire was completed (not reported here).

On days 2-5 of the CTC, the drinks containing the tyrosine and placebo compounds were ingested between 0700 and 0800 h. On day 6 of the CTC (when the post-test session took place), the drinks were ingested between 0200 and 0300 h. All drinks were supplied by the group commanders, which made it possible to control compliance.

The post-test session took place on day 6 of the CTC, between 0500 and 0800 h. A classroom in the barracks, close to the training ground, served as the testing room. The protocol was similar to that used in the pre-test session.

Combat training course (CTC)

The aim of the CTC was to enhance stress tolerance and to increase operational effectiveness. During the two-week CTC, the Ss had to cope with a range of physically demanding and psychologically stressful conditions, including sleep deprivation and food rationing. During the CTC, the limits of physical endurance were reached. Stress was not only induced by the severity of the demands, but also by their unpredictability. The diet of the Ss was restricted and controlled throughout the CTC. The last meal before the post-test session was provided between 1900 and 2000 h (i.e., about 10-12 h before the last test and 6-8 h before the last experimental drink).

Supplementation

L-tyrosine was supplied in a 500-ml drink, consisting of orange juice in which 70 g of the diet powder PROTIFAR® (Nutricia, Zoetermeer, The Netherlands) was dissolved. This amount of PROTIFAR contains 42 g of proteins, including 2 g of tyrosine. In addition to tyrosine, 70 g PROTIFAR contains: alaline (1.5 g), arginine (1.5 g), aspartic acid (3.4 g), cysteine (0.4 g), glutamic acid (9.5 g), glycine (0.8 g), histidine (1.3 g), isoleucine (4.3 g), leucine (4.3 g), lysine (3.7 g), methionine (1.1 g), phenylalanine (2.1 g), proline (4.2 g), serine (2.6 g), threonine (1.9 g), tryptophan (0.6 g) and valine (2.7 g). The placebo group received a 500-ml mixture of orange juice, in which 67 g of FANTOMALT® (Nutricia) was dissolved. FANTOMALT is a diet powder consisting of 95% carbohydrates, and contains no protein. Both drinks contained the same amount of calories (255 kcal). The Ss were required to take one drink daily for a five-day period.

The group commander handed out the containers with the drinks. The containers were marked with a green of yellow spot; which colour each subject had to receive was marked on a list given to the group commander. Neither the group commanders, nor the Ss were aware which colour corresponded to which treatment[a].

Data analysis

With respect to the MCT, the numbers of correct and incorrect responses (excluding omissions) were averaged across all trials, resulting in a correct and an incorrect score for each subject. Average RMS tracking scores during the TT and the DT were determined by averaging the squared 30-s interval values, and by subsequently computing the root of the average. Average RMS scores were

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[a] *This unusual mode of administration was dictated by dose and dosage form restrictions imposed by the RNLA medical supervisor, who allowed only administration of tyrosine as naturally occurring in food. Hence, the L-tyrosine was not supplemented in pure form in this study, but in protein-rich powder (PROTIFAR) which contains, in addition to tyrosine, other amino acids. However, it should be stressed that none of these are known to be precursors of NE. Likewise, the placebo was not a pure placebo administration. However, it should be emphasised that FANTOMALT does not contain any amino acids and may therefore be assumed not to influence NE synthesis. A second restriction was that the investigators were not allowed to determine plasma amino acid levels.*

computed for each of the 14 30-s intervals, as well as for the entire 7-m task period (with the exception of the first and the last interval). CMT performance could not be assessed. This was due to the fact that, probably due to excessive fatigue, a majority of the Ss had forgotten the target letters during the task performance, thereby making any assessment of the counts useless.

Differences in the treatment effects between the tyrosine group and the placebo group were evaluated by one-way Analyses of Covariance (ANCOVA), with Group as the independent factor, and the pre-test score as the covariate. The RMS tracking scores during the successive 14 intervals were analysed via repeated-measures ANCOVA's with Group as the independent factor and Interval as the repeated measurement factor. Owing to the absence of any variation in TIT values during the pre-test session, only the TIT values of the post-test session were analysed, using one-way Analyses of Variance. Because several earlier studies had found tyrosine supplementation to improve cognitive performance during stress exposure[14, 15, 16], it was hypothesised that similar effects would be found in the present study. Accordingly, statistical tests were one-tailed, except for the 14 RMS scores. Because no specific hypotheses had been formulated with regard to the POMS scores, two-tailed statistical tests were employed for these variables.

Results

Cognitive task performance

During post-test, the cognitive task performance of the tyrosine group appeared to have been less affected by the fatigue and stress induced by the CTC than that of the placebo group. On the MCT, the number of correct responses was higher in the tyrosine group than in the placebo group ($F(1,18) = 4.11$, $p < 0.05$; see Figure 1).

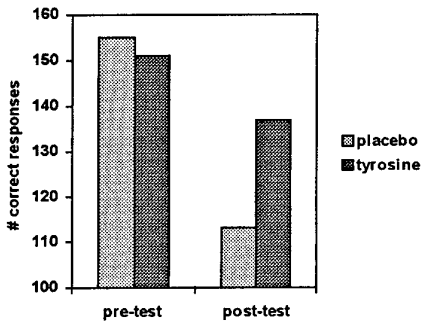

Figure 1. Memory comparison task: mean number of correct responses for the placebo (n = 11) and tyrosine (n = 10) groups during pre-test and post-test.

On the other hand, the difference in the number of MCT errors of both groups did not reach significance (see Figure 2).

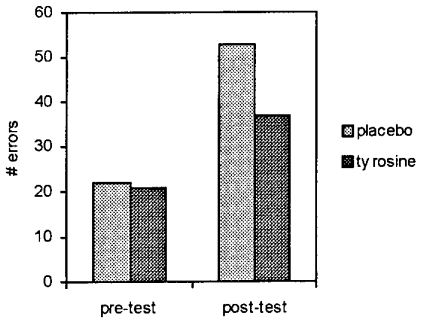

Figure 2. Memory Comparison Task: mean number of errors for the placebo and tyrosine groups during pre-test and post-test.

During the post-test, the tyrosine group also had a better RMS tracking score on the TT than the placebo group ($F(1,18) = 6.14$, $p < 0.05$; see Figure 3).

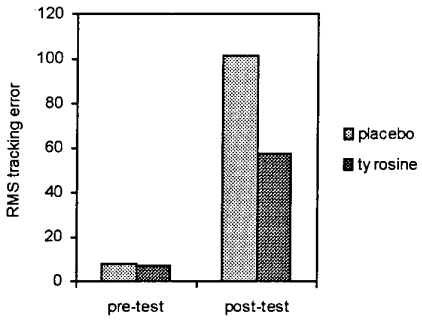

Figure 3. Tracking Task: mean root mean square (RMS) tracking scores for the placebo and tyrosine groups during pre-test and post-test.

The mean RMS values for the 14 successive 30-s intervals of the TT are presented in Figure 4. The ANCOVA yielded a marginally significant interaction between Groups and Intervals ($F(13,234) = 1.64$, $p = 0.08$). This suggests that,

as the TT progressed, the tyrosine group performed increasingly better than the placebo group.

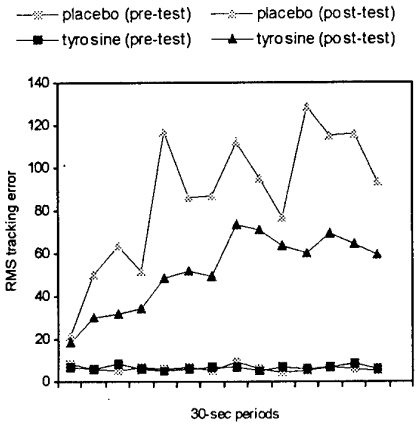

Figure 4. Tracking task: mean root square (RMS) tracking scores for each 30-s period for the placebo and tyrosine groups during pre-test and post-test.

The results concerning the percentage of task interruption time (TIT) in the TT are presented in Figure 5. The post-test TIT for the tyrosine group was lower than that for the placebo group ($F(1,18) = 5.10$, $p < 0.05$), suggesting that the tyrosine group suffered less from lapses of attention than the placebo group.

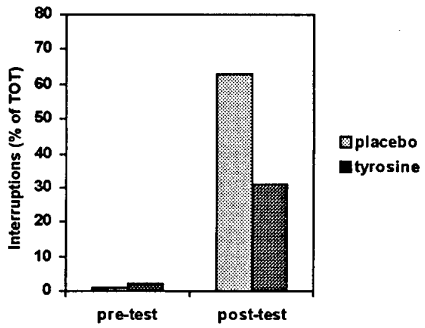

Figure 5. Tracking task: mean percentage of task interruption time (TIT) for the placebo and tyrosine groups during pre-test and post-test.

With respect to the DT, no significant difference emerged between the RMS tracking scores of both groups during the post-test (see Figure 6).

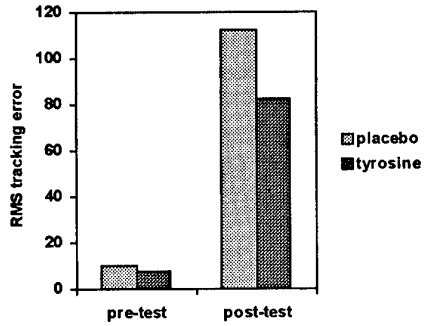

Figure 6. Double task: mean root mean square (RMS) tracking scores for the placebo and tyrosine groups during pre-test and post-test.

In contrast, the ANCOVA on the 14 separate interval values yielded a significant interaction between Groups and Intervals ($F(13,234) = 2.16$, $p < 0.05$; see Figure 7), indicating that, compared to the post-test performance of the placebo group, the post-test performance of the tyrosine group improved over time.

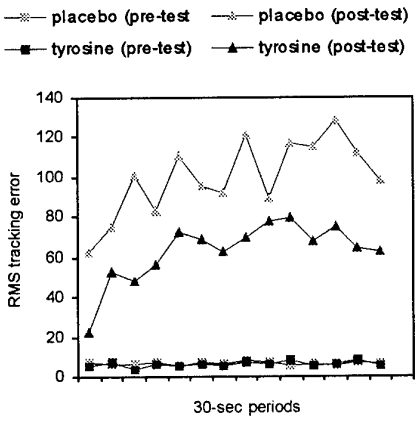

Figure 7. Double task: mean root mean square (RMS) tracking scores for each 30-s period for the placebo and the tyrosine groups during pre-test and post-test.

The DT task-interruption values of both groups are presented in Figure 8. There emerged a marginally significant Groups effect ($F(1,19) = 2.78$, $p = 0.06$), indicating that the placebo group tended to suffer more from attentional lapses during post-test than the tyrosine group.

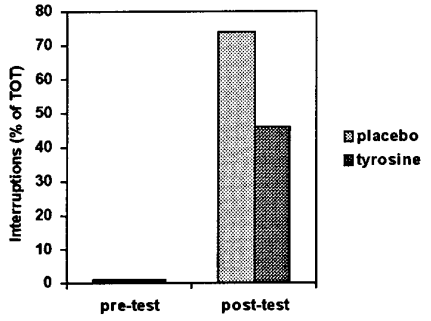

Figure 8. Double task: mean percentage of task interruption time (TIT) for the placebo and tyrosine groups during pre-test and post-test.

Questionnaire

The mean scores for both groups during pre-test and post-test, as well as the results of the ANCOVA's, are presented in Table 1[b]. During the post-test, there were no significant differences between the groups on any of the scales. However, t-tests revealed that there were several differences in the pre-test and post-test POMS values, suggesting effects that were due to the demands of the CTC. During post-test, the Fatigue score was higher than during pre-test (pre-test: 3.9 ± 3.0; post-test: 14.3 ± 5.2; $t(12) = -7.82$, $p < 0.001$). On the other hand, the Vigor score was lower during post-test (pre-test: 12.5 ± 4.6; post-test: 8.1 ± 4.7; $t(12) = 4.34$, $p = 0.001$). In addition, the post-test Tension score was higher than the pre-test value (pre-test: 2.6 ± 2.9; post-test: 5.1 ± 2.1; $t(12) = -2.65$, $p = 0.02$).

TABLE 1
QUESTIONNAIRE SCORES OF THE PLACEBO (n = 7) AND TYROSINE (n = 6) GROUPS DURING PRE-TEST AND POST-TEST

POMS Subscale	Group	Pre-test	Post-test	ANCOVA
Depression	Placebo	0.28	2.14	n.s.
	Tyrosine	3.33	2.50	
Fatigue	Placebo	3.71	14.00	n.s.
	Tyrosine	4.17	14.67	
Vigor	Placebo	14.43	8.71	n.s.
	Tyrosine	10.33	7.33	
Anger	Placebo	2.71	6.00	n.s.
	Tyrosine	5.67	6.67	
Tension	Placebo	2.42	5.71	n.s.
	Tyrosine	2.83	4.50	

[b] *Only 13 questionnaires (placebo group: 7; tyrosine group: 6) were returned by the Ss.*

Discussion

The aim of this study was to examine whether daily supplementation of a tyrosine-rich drink during a highly demanding combat training course (CTC) would reduce the effects of stress and fatigue on cognitive task performance and mood.

During the post-test session, which took place six days after the start of the CTC, and five days after the tyrosine supplementation began, the tyrosine group was found to perform not only better on a cognitive task (the memory comparison task (MCT)), but also on a perceptual-motor motor task (the tracking task (TT)). Only on the double task (DT), no significant difference between the overall RMS tracking scores of the two groups emerged (although the difference between the means of both groups was in the expected direction). However, as is suggested by the significant finding concerning the RMS values for the separate 30-s periods, there was a difference in the performance of both groups on the post-test DT, although this apparently emerged only gradually in the course of the task. The absence of a difference in the overall RMS tracking scores can probably be explained by increased error variances that were due to a reduced motivation associated with the time of presentation of the DT (it was the last task that was presented).

These findings seem to be supportive of the hypothesis that supplementation of tyrosine might serve to reduce the detrimental effects of stress and fatigue on cognitive performance during highly demanding sustained operations. During post-test, the performance on the MCT and the TT was better in the tyrosine group than in the placebo group. Moreover, there were indications that the performance difference between the groups increased as the tasks continued. Furthermore, the percentage of time the Ss were unable to perform the TT was larger in the placebo group than in the tyrosine group. There was a tendency in the same direction in the DT. This strongly suggests the supplementation of tyrosine may be effective in preventing attentional lapses due to fatigue.

These findings can be accounted for by the action of tyrosine which, as a precursor of NE, serves to prevent the depletion of NE in the brain[14, 15, 16]. However, this interpretation is complicated by a number of methodological complications that were due to the restrictions imposed by the RNLA medical supervisor. First, the possible influence of tyrosine on noradrenergic brain activity could not be directly evaluated by assessing plasma amino acid levels. Second, the dose of tyrosine that was administered in this study (2 g) was considerably lower than the standard dose

of 100-150 mg/kg (i.e., ± 6-12 g)[14, 15, 16]. Probably of more importance is the fact that the tyrosine was not administered in a pure form, but in a protein-rich mixture. As a consequence, several large neutral amino acids (LNAA's) were present in high quantities in the mixture, in particular (iso)leucine, phenylalanine and valine. There is no doubt that these LNAA's have competed with the tyrosine to cross the blood-brain barrier, and it can not be ruled out that they had an additional influence on brain functioning. However, it should be emphasised that stress- and fatigue-induced depletion of NE can only effectively be prevented by a precursor of NE, i.e., by L-tyrosine. Hence, it seems highly likely that the tyrosine, and not the LNAA's, was the most crucial factor in the observed reduction of the negative effects of stress and fatigue on cognitive performance.

Another issue that needs to be addressed is the possibility that the placebo drink had an adverse effect on cognitive functioning. Because the protein-rich drink had a high calorie value, it was decided to employ a placebo drink consisting of carbohydrates containing an equivalent amount of calories. Although this was not a real, and certainly not an ideal placebo, it was assumed that this drink, which could not affect NE synthesis, would have no effect on cognitive functioning. However, it has been suggested that carbohydrate consumption may result in a relative increase in LNAA TRP, which may be followed by an increased serotonin synthesis and release, and which may adversely affect cognitive functioning[3]. However, the studies that have examined the relationship between brain serotonin and carbohydrate meals have only employed rats, no humans[27]. Indeed, it is well established that carbohydrate meals raise brain tryptophan and serotonin in rats with empty stomachs. However, a recent review on animal and human studies concludes that any effects of carbohydrate meals on human brain serotonin are likely to be negligeble[27]. Furthermore, regarding dietary effects on behavioral measures, several studies[28, 29, 30] did not find any effect of carbohydrate meals on mood and performance. Hence, these studies do not seem to support the suggestion that the placebo drink did impair cognitive functioning.

The present study provided no evidence that supplementation of tyrosine was effective in reducing the effects of the stress and fatigue on subjective well-being. However, when evaluating this apparent discrepancy between the objective and subjective findings, it should be emphasised that only 13 out of the 21 Ss returned the questionnaires. Hence, the subjective data that were obtained could, unfortunately, hardly be regarded as representative. The only firm conclusion that can be drawn from these data would seem to be that the CTC did indeed, as expected, cause a substantial increase in fatigue and tension, as well as a decrease in vigor. As such, the subjective data may serve to underpin the fact that the CTC indeed posed considerable demands on the cadets.

Although the possibility that other amino acids than tyrosine might have contributed to the observed effects cannot entirely be ruled out, the present findings do seem to support the hypothesis that supplementation of tyrosine may serve to reduce cognitive impairment due to psychoenvironmental stress and fatigue. As such, they confirm earlier findings, obtained in laboratory studies. Moreover, they also strongly suggest that tyrosine supplementation can be effective in preventing cognitive degradation in highly demanding military operational environments that include sustained operations, as well as physical and psychological stressors. In particular, the results seem to indicate that not only the efficiency and speed of short-term memory operations can, to some degree, be protected against deterioration due to factors like stress and fatigue, but also, and maybe more importantly, that the degree to which these factors cause lapses of attention, can be considerably reduced. Overall, the cognitive impairment that was caused by the CTC in the placebo group appeared to be reduced by the supplementation of tyrosine by up to 40%.

Finally, it should be emphasised that, due to several methodological constraints, this study had a preliminary character. Hence, the present findings need replication in order to be draw definite conclusions concerning the efficacy of tyrosine supplementation in operational environments. First, it is necessary to evaluate the effects of tyrosine supplementation without the dose and dosage form restrictions that were imposed on the present study. Furthermore, it should be noted that the tasks that were employed addressed only quite basic aspects of cognitive functioning. Subsequent studies should therefore also include tasks that involve higher-order cognitive functions, including decision-making processes.

ACKNOWLEDGEMENT

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Sleep and Alertness Management During Military Operations: Questions To Be Answered

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Summary
Sleep and alertness management is a major point of attention for the medical support of military round the clock operations. Crew's awareness on the effects of fatigue and sleepiness should be enhanced. Flight surgeons should be trained on the use of practical methods to prevent serious fatigue and to enhance performance and alertness of the crew. Although, in civil and in military aviation a considerable number of studies have been conducted on fatigue countermeasures and preventive strategies, results are not readily available for practical use by flight surgeons. In order to develop useful guidelines for flight surgeons and crew, the international aeromedical research community should be able to produce a database on what is already known and identify areas where knowledge is lacking. In this context research questions related to the use of strategic naps, hypnotics, stimulants, and chronobiotic treatment are put forward.

1 Background

Military round the clock operations are characterized by circadian disruptions, rapid work shift changes, prolonged duty overnight, sleep loss, and high stress levels. These factors may result in high levels of fatigue and sleepiness when on duty, with consequent reduction of operational effectiveness and safety. Inadequate sleep facilities and mission stress further contribute to serious sleep deprivation (1), which is known to be an important cause of impaired performance of aircrew (e.g. 2, 3, 4, 5). Therefore, prevention of sleep loss and fatigue is a major point of attention in the medical support of a mission. Although several strategies for sleep-wakefulness management are available, many flight surgeons are not trained in the management of these problems. Moreover, useful information on the use of medications or other strategies is often not available at the deployment sites. In this context, it is important to provide flight surgeons with practical information and tools to prevent serious fatigue and sleep deprivation in their crews. In order to develop useful guidelines, it will be necessary to evaluate established strategies as used during the South Atlantic Campaign (6) and Operations Desert Shield and Storm (7) and to assess the usefulness and applications of recently developed preventive strategies and countermeasures.

The usefulness of preventive strategies and countermeasures has to be assessed in the light of the military scenarios in which they might be needed. Therefore, information and feed back from the operational commanders is indispensable for medical research teams.
In practice, the Royal Netherlands Air Force (RNLAF) is confronted with the following scenarios, which potentially cause impaired performance and alertness of the crew:

- Missions in the evening and night. Crew has to sleep during the day, when their body clock dictates wakefulness. In many cases this sleep will be short and disrupted (8). Moreover, sleep during the day will further be hindered by inadequate sleep facilities (e.g. noisy activities at the site).

- Very early missions, taking place when the circadian performance rhythm is in its trough (3-6 a.m.). Sleep preceding such missions is characterized by short total sleep times and impaired quality (5, 9). Crew often try to anticipate very early rising by going to bed in the early evening. However, their sleep efficiency is often impaired and sleep latencies are long.

- Critical activities directly following transmeridian deployment, with consequent jet lag symptoms, impaired performance, and increased daytime sleepiness in the first days after arrival in the new time zone (10).

- Sustained missions during which performance and alertness have to be preserved for a long time period. In most cases, sustained missions are characterized by shift work. It takes some days before the sleep-wakefulness rhythm has adapted to changes from day to night shifts (8). During sustained missions cumulative fatigue is caused by cumulative sleep debt and mission stresses (11, 12, 13).

In the above-mentioned scenarios sleep management plays an important role. General and specific measures are necessary to prevent serious fatigue and sleep loss

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in crews. In most cases general measures will include proper preparation of the mission, optimization of sleep facilities, and adequate support of crew with regards to mission stress and individual problems. More specific measures are needed to optimize performance and alertness. These specific measures include planning of sleep periods and strategic naps, induction of sleep at times when the body clock dictates wakefulness, antagonizing sleep inertia and/or residual effects of hypnotics, stimulating performance and alertness at times when the body clock dictates sleep, and accelerating entrainment after transmeridian deployment.

2 Operational issues to be studied

In civil aviation, research has been focused mainly on non-pharmacological strategies, while in the military environment, research on the pharmacological approach has predominated. Extensive research has been already performed as well in civil aviation as in the military. However results are not readily available for practical use by the flight surgeon. The aeromedical research community should be able to draw guidelines from what is already known and identify areas where knowledge is lacking.

In order to develop practical guidelines to be used by flight surgeons during mission preparation and at the deployment site, the Ministry of Defense of The Netherlands commissioned research on the following issues:

Short sleep periods and mission effectiveness

Operations during late evening or night require a minimum of sleep prior to the mission. Because the circadian phase does not allow for sleep, this daytime sleep has to be facilitated pharmacologically in most cases. Furthermore, proper measures should be taken to reduce sleepiness after waking up and stimulate alertness during the night. Sorties at dawn (3-6 a.m.) also have their specific problems, as pre-duty sleep is often too short and crews have to start when their body clock still dictates sleep. Both scenarios require pharmacological induction of sleep, "assisted awakening", and alertness enhancers to preserve performance and alertness during the mission. In addition, the use of short naps has to be considered.
During extended missions, cumulative sleep deprivation will occur when daily sleep times are too short. Critical sleep deprivation is known to impair performance and alertness and to reduce mental and physical fitness.

Mission effectiveness and jet lag / change to night shift

Optimal performance after transmeridian deployment requires rapid adaptation to the new time zone and measures to counteract the effects of jet lag. In addition to using the local Zeitgebers, entrainment might be accelerated by the use of melatonin and bright-light (alone or in combination) and performance and alertness can be enhanced by pharmacological means. This approach, with the addition of strategic naps and hypnotics, might also be used to preserve sleep and alertness when crews change from day to night shift.

3 Questions to be answered

3.1 Inter-individual differences

Studies concerning the effects of shift work and jet lag, and recommendations on fatigue countermeasures seldom take into account inter-individual variability. However, it is common knowledge that people differ considerably in their capacities to sleep at unusual times of day or to sleep in a hostile environment. Inter-individual differences are also found in sensitivity for the effects of transmeridian travel and shift work, and the effects of countermeasures such as melatonin, hypnotics, alertness enhancers, and strategic naps. In a study on the effects of a controlled rest on the flight deck on performance and alertness in 59 airline pilots, it was found that a 40-minute nap in the cockpit seat significantly improved performance and alertness up to top of descent (14). Although this beneficial effect was statistically significant, for some pilots the nap had no effect and a minority even showed impaired performance and alertness for a longer time after the nap. Although this minority has no statistical consequences, these few affected pilots might have detrimental effects on mission effectiveness and safety. Therefore, when recommending the cockpit nap, it was emphasized that those pilots, for whom such a nap will be disadvantageous, should be enabled to identify themselves. For this purpose, military crew should be educated to identify their personal characteristics and to enhance their awareness of causal relationships between sleep, fatigue, performance, and alertness. In civil aviation, a "Fit-to-Fly Checklist" has been developed for that purpose (15), which is tailored to the needs of airline pilots (and as such not applicable to aircrew engaged in military operations).

Furthermore, tools should be developed to enable flight surgeons and commanders to identify individual characteristics of pilots and other professionals with highly critical tasks. Flight surgeons could collect useful information during training missions involving transmeridian deployment and/or shift work. Information should minimally include "baseline" individual characteristics, such as age, morning/evening type, good/poor sleeper, adaptability to shift work, capacity to nap, duration of sleep inertia, and past experience with jet lag, melatonin, hypnotics, and stimulants. In addition, during a deployment, subjective data on sleep-wakefulness patterns, alertness/sleepiness during duty, and (cumulative) fatigue can be collected, using sleep logs. Ideally, objective data on sleep-wakefulness patterns

(actigraphy) and a circadian marker should complement subjective data, but this might not be feasible during an intensive deployment. It should be considered to use a pocket-size computer for data-logging. This method has been extensively used in field studies in civil aviation (5, 14) and has proven its practicability. Data from the personal "pocket-computer" can be downloaded into a PC at the deployment site, enabling easy access to data for the flight surgeon or commander. Using above-mentioned information, flight surgeon and crew can determine the best possible strategy to prevent serious fatigue and to preserve performance and alertness during the mission.

Commanders should also be provided with data on the cumulative sleep debt of themselves and their subordinates. Up to now, commanders often lacked this information and therefore could not estimate the impact on individual and unit effectiveness that lack of sleep would have over the next few days (13). Therefore, an easy method to measure (cumulative) sleep duration (sleeplogs, actigraphy) should be developed for use in a military environment.

3.2 Strategic napping

The effectiveness of short naps (0.5-3 hrs) to counteract fatigue and to prevent inadvertent sleeping during duty has been evidenced by many authors (e.g. 14, 16, 17, 18). When circumstances permit, a strategic nap of 1-2 hrs should be considered as a countermeasure to fatigue and sleepiness. It has been found that performance and alertness improve as a function of sleep duration (19, 20). In general, longer naps are not recommended because these might interfere with the normal sleep-wake rhythm. Inter-individual differences have to be taken into account, because some subjects will not be able to sleep at all (21) or remain drowsy for long time periods after the nap. When naps are planned at times when the body clock dictates wakefulness, pharmacological sleep induction has to be considered. An important question to answer is the duration of sleep inertia after a nap. It seems likely that sleep inertia can be shortened by instructing the napper to follow the normal "morning routine" after awakening (e.g. take a shower, brush teeth, have coffee and breakfast). However, this is questioned by Jewett, Wyatt, Ritz-de Cecco et al. (22), who found no effects of going out of bed, breakfast, or showering on the duration of sleep inertia. After a 40-min controlled nap in the cockpit seat, sleep inertia was estimated to last less than 15 minutes on average (14, 17). However, duration of sleep inertia was not explicitly assessed in these studies. In contrast, Caldwell & Caldwell (23) found that postnap grogginess persisted for about 2 hours after a 2 hour nap taken at 21:00 hr. Although this long sleep inertia might be related to the time the nap was taken, this finding might have important consequences for the planning of naps.

In summary, in the context of strategic napping the following questions should be addressed in future studies:

- necessity and feasibility of pharmacological induction of sleep for daytime naps
- duration of sleep inertia after naps of various duration and at various times of day
- effectiveness of stimulants and/or bright light in reducing sleep inertia after a nap
- combination of short naps and stimulants and/or bright light to enhance performance and alertness

3.3 Induction of sleep

Although the ideal hypnotic for aircrew engaged in military missions does not exist, hypnotics are probably essential to preserve sleep under difficult conditions. Nicholson (6) reported that 20 mg temazepam (the rapidly absorbed formulation) was useful in helping aircrew acquire sleep at irregular times of the day during the South Atlantic Campaign. There is sufficient evidence that the rapidly absorbed formulation of temazepam is free of residual effects on performance and alertness as measured 8 hours after ingestion (24, 25). This also applies for the triazolo-thienodiazepine brotizolam (25, 26), which compound is not marketed in The Netherlands. Both hypnotics are aimed at the preservation of a 7-8 hour sleep. During intensive and sustained operations it is often necessary to ensure sleep during shorter time periods, and the question is whether temazepam and/or brotizolam are free of residual effects 5-6 hours after administration. In this context zolpidem, an imidazopyridine with a short elimination half-life (2.4 hrs on average), is to be considered as an alternative. It was found that 10 mg zolpidem increased effectiveness of a 2 hour nap, whereas performance and alertness measured 4½ hours post-administration showed no differences between zolpidem and placebo (23). There is evidence that 10 mg zolpidem is free of residual effects from 6 hours after ingestion (27, 28). However, the issue of sedative residual effects still needs further study with special reference to the occurrence of residual effects in females using zolpidem.

For practical use, the question remains whether zolpidem 10 mg has an advantage over temazepam (10-20 mg), of which the use in aircrew is well established during the past decades. When answering this question, it has to be taken into account that residual effects, if any, might be completely counteracted by a stimulant drug that will be administered to crewmembers after the wake up call.

The very recently developed non-benzodiazepine zaleplon has a half life of approximately 1 hour and is advocated by the manufacturer as a sleep inducer for people with transient insomnia and sleep disturbances associated with time zone shifts or shift work schedules.

It appears to facilitate falling asleep but the effect on total sleep time is unclear (29). Dietrich, Emilien and Salinas (30) showed that 8.5 to 12.5 hours after ingestion of 5 or 10 mg zaleplon residual effects did not significantly differ from placebo, while 7.5 mg zopiclone showed significant sedative effects. This was confirmed by O'Hanlon, Vermeeren, Fournie & Danjou (31), who found no evidence for residual effects 5 to 6 hours after the last dose of 10 or 20 mg zaleplon. These results justify further consideration of zaleplon in the context of transient insomnia of military crew. Although zaleplon is not a benzodiazepine, it binds to the $GABA_A$-benzodiazepinereceptorcomplex. Therefore, it should be taken into account that adverse reactions such as rebound insomnia, anterograde amnesia and hazardous behaviour shortly after ingestion, might occur as frequently as in the 'ultra-short benzodiazepine' group. The frequency of these reactions is not known, because the compound has only recently appeared on the market.

In summary, in the context of hypnotics the following questions should be addressed in future studies:

- residual effects of temazepam 5-6 hrs after administration
- residual effects of zolpidem 5-6 hrs after administration in females
- comparison of zolpidem 10 mg with temazepam (10-20 mg) for induction of sleep of various duration (2 - 4 - 6 hrs)
- usefulness of zaleplon in the military environment
- effectiveness of stimulants and/or bright light in counter-acting residual effects of hypnotics

3.4 Melatonin

Hypnotic properties

In the context of induction of daytime sleep during intensive military operations, the usefulness of exogenous physiological or supra-physiological doses of melatonin is a matter of discussion. Results of various studies on the sleep inducing properties of melatonin are difficult to compare because of large differences in doses (range 0.1-250 mg) and assessment methods. Moreover, it is known that there is considerable inter-individual variability in endogenous melatonin production and in dose-response and distribution rates of exogenously administered melatonin.

Although it was observed that melatonin administration during the day produces more consistent reductions in sleep latency than does nocturnal administration (32), some results from studies on the efficacy of melatonin after night-shift work were disappointing (33, 34). Moreover, the sleep promoting action in insomniacs with *non-circadian* sleep disturbance has not been convincingly evidenced (35). Melatonin might be considered as a gentle promoter of general relaxation and sedation, which -in favorable conditions- might facilitate sleep onset (36). However, when efficient (daytime) sleep induction in military crew is pursued, hypnotics such as temazepam or zolpidem appear to be more efficacious than melatonin.

Phase shifting properties

It appears that in military settings melatonin's chronobiotic effects are more important than its hypnotic properties. There is sufficient evidence that exogenous melatonin, when suitably timed, is able to accelerate adaptation to phase shift in both field and simulation studies of jet lag and shift work (37). However, most studies employed volunteer travellers who, unlike military crew, were free of duties at their destination. Studies in aircrew on duty showed less favorable results (38). Disappointing results might be caused by subjects receiving melatonin treatment at an inappropriate circadian phase, as there is evidence that the timing of melatonin administration is fairly critical. Moreover, it has to be taken into consideration that there is large inter-individual variability in the phase-shifting properties of exogenous melatonin.

Adaptation should not be pursued during short missions and/or rapid shift rotations. However, in other cases of transmeridian deployment acceleration of adaptation will be beneficial. When the aim is to accelerate adaptation after transmeridian deployment, melatonin is recommended as first choice treatment. However, there is discussion about the usefulness (and recommended duration) of pre-travel treatment (38, 39, 40), duration of post-travel treatment, timing of melatonin, and whether physiological (0.3-0.5 mg) or pharmacological (5-10 mg) doses should be recommended (36, 37, 41).

With regards to the application of melatonin as chronobiotic in a military setting, the following questions should be addressed in future studies:

- physiological or pharmacological dose?
- usefulness of pre-travel treatment
- post-travel treatment: timing of melatonin
- post-travel treatment: duration

3.5 Bright light

Phase shifting properties

It is well accepted that bright light exposure can influence both the amplitude and phase of human circadian rhythms, and there is growing evidence that light may affect human physiology and behavior through non-circadian rhythms as well (42). Scheduled exposure to bright light can alleviate jet lag symptoms by accelerating circadian reentrainment to new time zones (43). Laboratory simulations, in which sleep is advanced by 6 to 8 hours and the subjects exposed to bright light for 3 to 4 hours during late subjective night on 2 to 4 successive days, have produced conflicting results. Field studies had encouraging results, but their

applicability to military operations remains uncertain due to limited sample sizes (e.g. 44, 45, 46). One field study with a somewhat larger number of subjects, found that exposure to bright light in the morning appeared to facilitate the consolidation of sleep into a single nighttime episode (47). When bright light is used to accelerate adaptation to phase shift, the timing, duration, and intensity of light exposure are critical. In this context it is interesting that Martin & Eastman (48) found no difference in phase shifting efficacy between exposures with 5700 lux 3 hrs/day or 1230 lux 3 hrs/day. To facilitate adaptation after transmeridian deployment, a combination of exogenous melatonin and bright-light at antiphase seems a promising opportunity.

Alertness promoting properties

The alertness promoting properties of bright light exposure have been described by many authors (e.g. 49, 50, 51). Therefore, the efficacy of bright-light to shorten sleep inertia and to promote alertness during night shifts should be assessed in a military environment. To preserve alertness during long nightly duty hours the usefulness of combinations of bright light and a stimulant should also be assessed. A combination of bright light and caffeine appears to be useful (52), although in this study, as in most bright light/night shift studies, subjects were exposed to bright light during the entire night. This will often be impossible in military scenarios, where bright light can only be administered for limited time periods (e.g. 0.5 hr). The method of administration of bright light at the deployment site should also be a matter of concern. Illumination of a group sleep facility with light of sufficient intensity might be impracticable. Experiences of civil aircrew with small individual light sources, such as the Light Visor, are ambiguous as a number of users complain about irritating effects.

With regards to the application of bright light in a military setting, the following questions should be addressed in future studies:

in general:

- adverse effects (safe wavelength(s)?)
- most acceptable method to expose crew

phase shifting properties:

- optimal times for light exposure on the first as well as on subsequent treatment days
- optimal intensity and duration of exposure

alertness promoting properties:

- efficacy of short duration exposure
- optimal intensity
- usefulness of combination bright light and stimulant
-

3.6 Stimulants

Although everything possible should be done to prevent (cumulative) sleep deprivation, severe fatigue and sleepiness on the job will inevitably occur during military round the clock operations. Therefore, use of pharmacological stimulants will be necessary to optimize performance and alertness during nightly and/or lengthy missions. Moreover, stimulants might be needed to minimize sleep inertia and the residual sedative effects of hypnotics.

Dextroamphetamine

The efficacy of d-amphetamine 5 mg for the short-term sustainment of alertness and performance of sleep deprived aircrew, has been established (e.g. 7, 53, 54). However, future field studies should assess the usefulness and side-effects of longer-term use of dextroamphetamine. Because of potential adverse effects, such as subjective euphoria, sympathomimetic effects, insomnia, tolerance, and dependence, use of amphetamine by military crew has been a matter of disagreement. Although the frequency of side-effects of d-amphetamine, when properly used, appears to be low (7, 54), use of amphetamine is not allowed in the RNLAF.

Pemoline

Pemoline has a unique chemical structure that includes a heterocyclic ring system incorporating a substituted side-chain of amphetamine. Pemoline has been successfully used for treatment of narcolepsy and attention-deficit hyperactivity disorder (ADDH). It is a dopamimetic agent that is relatively free of sympathomimetic activity and dependence and has the potential to improve alertness and performance in rested and sleep deprived subjects. In healthy volunteers, who were studied under realistic operational circumstances, it was found that 20 mg pemoline was able to maintain nocturnal performance without having adverse effects on recovery sleep (55). The potential of pemoline justifies further study. However, future studies might be hindered by the fact that pemoline has recently been removed from the market, due to cases of serious adverse events in children.

Modafinil

Recently the eugregoric synthetic stimulant modafinil has been promoted as an alternative for amphetamine (56, 57, 58). It was found that it is as effective as amphetamine with far fewer side effects, such as sympathomimetic activity and dependence. However, Baranski & Pigeau (59) found an "overconfidence" effect of modafinil when compared to d-amphetamine and placebo. This finding is reason for concern and therefore the relation between the subjective and performance enhancing effects of modafinil should be clarified.

Modafinil is now marketed in USA and Europe for treatment of narcolepsy. Questions to be answered regarding the usefulness of modafinil to stimulate alertness and performance in military scenarios concern:

- a more comprehensive understanding of the relation between its subjective and performance enhancing effects (overconfidence effect)
- effects of long term administration: side-effects and development of tolerance.
- comparison of modafinil and d-amphetamine: advantages?
- comparison of modafinil and pemoline: advantages?

Caffeine

In the RNLAF, the only approved stimulant is caffeine. Caffeine has been widely used as a psychostimulant. It is easily accepted and safe, when properly used. Bonnet and Arand (60) showed the usefulness of 200 mg caffeine administered after a 4 hour nap followed by 24 h sleep deprivation. In general, the stimulating effects on alertness and performance appear to be transient and drug tolerance develops easily. Effects of caffeine show large inter-individual variability, primarily dependent on the chronicity of its use. Side-effects with higher doses or in caffeine naive subjects are palpitations, tremors, disturbed sleep, and anxiety.

Recently a slow release caffeine (SR Caffeine) has been developed, which has shown to be effective in enhancing alertness and performance in sleep deprived subjects (61). Because the use of caffeine is widely accepted, it seems useful to conduct further research on SR Caffeine, with special reference to:

- establishing the advantage of SR Caffeine over normal caffeine
- long-term side-effects
- development of tolerance with prolonged administration.

4 Conclusion

Sleep and alertness management is a major point of attention for the medical support of military round the clock operations. Crew's awareness on the negative effects of fatigue and sleepiness on performance and alertness should be enhanced and flight surgeons should be trained on the use of practical methods to prevent serious fatigue and to enhance performance and alertness of the crew. Practical methods include use of strategic naps, hypnotics, stimulants, and chronobiotic treatment. Although, both in civil and in military aviation a considerable number of studies have been conducted on these issues, results are not readily available for practical use by the flight surgeon. In order to develop useful guidelines for flight surgeons and crew, the international aeromedical research community should be able to produce a database on what is already known and identify areas where knowledge is lacking. In this context, it is recommended to study the usefulness of recently developed hypnotics and stimulants, and chronobiotic treatment, such as melatonin and bright light in larger field studies in a realistic military setting. Research programs should also take into consideration potentially useful combinations of treatments, such as hypnotics with stimulants and/or bright light and melatonin with bright light at antiphase.

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ACUTE AND DELAYED EFFECTS OF MELATONIN : OPERATIONAL SIGNIFICANCE

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Summary
The primary function of melatonin in mammals is to convey information about the changing length of the night in the course of the year. Melatonin appears not to be essential for circadian organisation but reinforces functions associated with darkness. In diurnal humans this of course included sleep and lowered body temperature. It may act as an adjunct to light for the maintenance of synchrony with the solar day. Exogenous melatonin can both advance and delay the timing of sleep and other circadian functions and appears to stabilise sleep to a 24h period taken daily at an appropriate time in free running conditions. However there is at yet little evidence that it can consistently synchronise free running strongly endogenous variables such as core temperature. Its effects on sleep in free run are complex, depend on circadian time of administration, and in part can be interpreted on a photoperiodic basis.

Introduction
In all eukaryotic species from microorganisms to humans melatonin is normally synthesized during the night (1) and its duration of secretion reflects the length of the night. In mammals its primary sites of production are the pineal gland and the retina, where it is derived from tryptophan via acetylation of serotonin to N-acetylserotonin and O-methylation of the latter to N-acetyl-5-methoxytryptamine (melatonin). The rhythm of pineal synthesis is generated in the suprachiasmatic nuclei (SCN) and synchronized to the 24h day primarily by the light dark cycle. In healthy volunteers the production in terms of amplitude, detailed profile and phase is very stable in the same individual from day to day. The rhythm is closely coupled to that of core body temperature. In humans the peak of melatonin and the nadir of temperature are in close coincidence and this relationship may be in part causal. The relationships of many sleep parameters to the core temperature nadir can thus in principle be applied to the peak of melatonin. The primary physiological function of melatonin is to transduce photoperiodic information for the organisation of seasonal and circadian physiology.

A number of drugs (1), posture (2) and exercise (3) will modify melatonin secretion, and sufficiently bright light will suppress production at night (4). However if these are controlled it is assumed, not unreasonably, that the phase of melatonin, or its urinary metabolite 6-sulphatoxymelatonin (1) reflects the phase of the endogenous clock in the SCN. This has led to the extensive use of melatonin as a 'circadian marker rhythm'.

The actions of melatonin as a possible endogenous circadian zeitgeber in humans have been much discussed (e.g. 5). Since its profile of secretion depends essentially on the light dark cycle it can only function endogenously as an adjunct to light in sighted humans. It has also been proposed as an endogenous sleep substance, as an opener of the 'sleep gate' in the evening, as 'nature's soporific' (6, 7, 8, 9). It is difficult to understand how a

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substance which is made at night in all species including nocturnal species can be 'natures soporific'- indeed this is the strongest possible argument against a universal sleep promoting role for melatonin.

Melatonin and sleep

Humans can sleep out of phase with endogenous melatonin, although their sleep may be shorter, have more wakefulness and be subjectively of poorer quality than when sleeping in phase (10, 11). It is remarkable that some free running blind subjects, whose peak melatonin will intermittently occur, depending on endogenous periodicity (tau), during the daylight hours, do not complain of sleep problems (although many others have sleep disorders related to free running rhythms), (12, 13, 14). Some of the best correlative evidence concerning an endogenous role for melatonin in human sleep comes from studies in free running blind or sighted subjects when maximum sleep propensity occurs closely associated with the peak of melatonin secretion and the trough of core temperature (15). In the case of blind subjects living in a normal environment this is particularly evident by the occurrence of daytime naps when melatonin peaks during the day (13). Further elegant correlative data from Lavie and co-workers suggests that the evening melatonin rise may open a 'sleep gate' (7).

Acute effects on sleep

There is no doubt that melatonin does affect sleep. The first evidence dates from 40 years ago when Aaron Lerner, who first isolated the substance, took 100 mg and described sleepiness after the dose (16). Early investigations used electroencephalographic (EEG) characteristics to delimit an acute mild sedative and 'hypnotic' effect in both animals (cats, rats, chickens) and humans, reviewed by Cramer in 1974, (17). Subsequently a substantial literature, generally using much lower doses, has described advance shifts in the timing of sleep after early evening administration, transient sleepiness at several different times of day within 2-4h of the dose, time dependent increases in sleep propensity, effects on the waking EEG comparable to, but not identical with, benzodiazepines, a lengthening of the first rapid eye movement (REM) episode after early evening administration, increases in the fast EEG frequencies after evening naps or night time sleep and 'beneficial effects' taken at bedtime. The latter are usually a reduction in wake after sleep onset (WASO) and an increase in total sleep time (TST) evaluated subjectively, by actigraphy and, rarely, by EEG. When melatonin was used to hasten adaptation to a 9h phase advance, TST, sleep efficiency and stage 2 sleep were increased whereas slow wave sleep (SWS) was decreased (18), but only on the first post phase shift day. The subject has been extensively reviewed recently (7, 19, 20, 21, 22). There is still inconsistency in the findings however and some studies have found no effects of any importance on sleep (e.g. 23). Differences between study conditions, subjects, dose and timing are likely to be the reason for apparently contradictory effects and much more information is needed for solid conclusions to be drawn.

Phase shifting effects of melatonin

Following an acute dose of melatonin (0.5 -10 mg) core body temperature declines and causal links have been suggested between this effect, the induction of sleepiness and, in the case of early evening administration, earlier sleep and a subsequent phase advance of melatonin onset (24, 25, 26, 27). Substance has been added to this speculation by the observation that both the temperature decline and the sleepiness are dependent on posture. Subjects who remain upright and/or active after the dose do not show either the sleepiness or the temperature drop (28). However the induced phase shift may not depend on changes in core temperature. In early work, subjects taking 2mg melatonin daily at 1700h for 30 days and remaining active only showed significant evening sleepiness after 4 days as a group (29, 30). Moreover in conditions where very little acute change in temperature was found, phase shifts still occurred (31).

It is our opinion that endogenous melatonin indicates dark onset (the rise) and offset (the decline) and reinforces physiological functions associated with darkness in humans as in other mammals. Pharmacological doses of melatonin may well act differently. What constitutes a physiological dose of melatonin remains problematic. In the authors' experience fast release doses of melatonin in corn oil/1% ethanol from 0.05 - 0.2 mg give, on average, 'physiological', i.e. night time plasma concentrations of melatonin during the day (24). Individual pharmacokinetics are extremely variable with plasma levels varying up to 25 fold and this may account for some of the variability in the literature (32, 33). For example even 2 mg can give rise to near physiological levels in a very few individuals

(30, 33). Evidently what is a physiological dose is individually variable.

Fast release melatonin (0.5 mg - 5mg, or less in divided doses) phase advances and delays the circadian system (endogenous melatonin, core temperature, sleep timing) according to a PRC (31, 34, 35, 36). In our experiments this is a dose related phenomenon for advance phase shifts in the range 0.05-5mg (24). The duration of endogenous melatonin may be increased by evening oral administration since the onset can be advanced more than the offset (30, 37), and in large enough doses the morning decline may be delayed. In this way the circadian and photoperiodic effects become confounded, if indeed they are distinguishable at all.

Delayed effects of melatonin: synchronisation of human circadian rhythms

Since melatonin does show the characteristics of a zeitgeber in that a PRC can be generated, it would be expected to entrain fully the circadian clock in suitable circumstances. Human tau appears to be on average 24.3h or less in constant dim light in sighted subjects (38, 39, 40) and thus the clock needs to be phase advanced on average by 0.3h or less each day. Acute phase shifts induced by melatonin in an entrained or free running environment are of at least this magnitude when sleep is permitted. However it is difficult to demonstrate entrainment in humans, with the exception of apparent entrainment ('stabilisation to 24 hours') of the sleep wake cycle (31, 41, 42, 43). Given to blind subjects free running in a normal environment melatonin (5mg) induces phase shifts and can stabilise sleep (especially sleep onset) in some subjects (42, 43). Very recent data using carefully timed melatonin shows that the circadian system can indeed be fully entrained in some but not all blind individuals (Lockley, Skene, Arendt, submitted for publication).

It is possible to maintain the circadian system of the majority of sighted subjects transferred to a free run in constant dim light (<8 lux) on a cycle indistinguishable from 24h by daily administration of melatonin (5 mg, 2000h) at 24h intervals for periods of 15 days (31). Less successful was an attempt to reentrain the same subjects after free running with different periodicities for 15 days in constant dim light by daily melatonin at the same clock time. The initial melatonin administration at 2000h occurred at different circadian phases. Both phase advances and phase delays of sleep and core temperature were seen according to a PRC. However the data indicated that the effects observed were complex and variable. Some subjects showed a stabilization of sleep onset with little effect on sleep offset for periods of several days. There was some evidence for splitting of sleep such that some components delayed and others advanced to resynchronise. One subject showed a double phase delay and sleep (but not core temperature) appeared to entrain to melatonin given at sleep offset for several days. Core temperature data indicated that tau was shortened, in one case to significantly less than 24h, rather than fully entrained, in many subjects. Since the time series was short (15 days) some taus indistinguishable from 24 h may well not have been synchronised. Similarly a longer study time might have shown synchronisation of temperature in more subjects. Only a very long time series would resolve these questions.

Most surprising of all in this free running study was a phenomenon of fragmentation of sleep in two subjects taking 5mg melatonin close to core temperature maximum immediately after transferring to a dim light environment. Cross-over from melatonin to placebo led to consolidated sleep. A subsequent attempt to time melatonin specifically to be close to core temperature maximum provided two further subjects showing fragmented sleep with melatonin compared to placebo (44). Thus, of a total of 16 subjects studied in dim light in this way, 4 showed sleep fragmentation. There was evidence by spectral analysis for the presence of two components with different periodicities in 3 of the 4 subjects.

Whatever the explanation it is clear that this phenomenon would be highly undesirable if consolidated sleep and alertness is required. However a strategy of splitting sleep into two components with melatonin may lead to more rapid adaptation to phase shift by advance of one and delay of the other component.

Melatonin can however maintain apparent entrainment (stabilisation to a 24 hour period) of sleep in most individuals. This may simply be a masking effect of acute sleepiness induced by the treatment. But some data is inconsistent with this hypothesis. Notably the fragmentation of sleep by melatonin in some free running individuals, as described above, is evidence against strong acute hypnotic effects. Similarly, taken during free running experiments during periods of minimum sleep debt, sleep does not necessarily follow the

treatment. The data in this case are more consistent with an effect on sleep timing. Since sleep can be apparently entrained in the absence of temperature entrainment this suggests that the mechanisms of sleep timing differ from those of strongly endogenous rhythms such as temperature. The differentiation of the central circadian clock in the SCN into discrete areas and the fact that SCN cells in culture each show individual periodicities supports this possibility (45, 46, 47).

Conclusions

The majority of published data indicate that melatonin has therapeutic benefits in circadian rhythm-related sleep disorders and adaptation to forced phase shift (22). However as yet its mechanism of action remains unclear, the appropriate dose for any given condition and individual is uncertain, the contraindications remain to be defined, there is virtually no data on long term safety, use with concomitant medication or organic disease and very little information concerning its most important function as a photoneuroendocrine transducer in humans. Since it appears to have some photoperiodic effects, and since in principle daylength has the potential to affect many if not all physiological systems, much further research is needed on its physiological role and pharmacological effects in humans.

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PORTUGUESE AIR FORCE AEROMEDICAL CENTRE APPROACH TO MANAGEMENT OF SLEEP/WAKEFULNESS OF AIRCREW

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1-Introduction

The first time we noticed that we had a problem with the lack of guidelines to manage the sleep/wakefulness disturbances among aircrew was during the time we had a P3-P stationed in Sigonnela (IT) flying integrated in a NATO force. They were there during periods of 15 days flying following a schedule that we can see an example in Figure 1.

According to this we sent there a flight surgeon that detected two major problems: the lack of regularity on shiftwork and overworkload.

We have to add to the hours we can see in the example, 3 more hours of pre-flight briefing and two hours of debriefing, all with only one crew. An additional problem was the location of the rooms of the NCOs, either air crewmembers or ground crew-members, situated near the flight line, submitted to high levels of noise and very difficult to get dark enough during the day, limiting a good or sufficient period of sleep.

All the personnel had difficulty to get asleep; this difficulty was fought in two ways, either one not really good: drink large amounts of alcoholic beverages or exercise near exhaustion.

After the survey we decided to propose to send a flight surgeon to stay with the crew for one deployment (15 days). During this stay he would brief the crew about the problems with shiftwork, sleep and fatigue and at the same time help them, if necessary, on the resolution of sleep problems. We thought to use temazepam as an aid to correct the sleep cycle, this authorization was denied.

The second situation we had the same problem was with the C-130 flying to Africa (mainly Angola and S. Tomé). Usually they leave Lisbon between 19:00 and 01:00. The total flight time is around 12 hours, what implies one night with less sleep or no sleep, although the crew is an extended crew (usually one more senior pilot).

In 1997 the Aeromedical Center with the Psychology Center decided to propose, again, a study on the subject of aircrew fatigue, but we are waiting for clearance to go ahead.

In 1999, April, we were alerted, by the F-16 detachment in Aviano that was questioned by the USAF Flight Surgeon about the portuguese policy on the use of hypnotics and stimulants

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on pilots. As we don't have any regulation concerning the subject I was sent to Aviano to talk with the Flight Surgeon. I was briefed on the USAF protocols. At that time we didn't make any trial with our pilots because they were already in operations.

The main problem we have in PoAF is the divorce of Flight Surgeons and the planning of military operations. This is a handicap that we are trying to overcome.

2-What we do now

During the CRM courses we give a lecture on "Circadian rhythms, sleep and fatigue".

In this lecture we explain what are the circadian rhythms, how they suffer alterations and the effects of those, the physiology of sleep and its alterations and definition and causes of fatigue and the means to fight against it. After the lecture that has a duration of about 50 minutes we give to the crewmembers a practical exercise, that they have to solve. The objectives are the detection by them of the situations that can produce fatigue, sleep deprivation and also circadian rhythms disruption, what are the effects of it and what solutions they propose.

All the flight surgeons stationed at the Air Bases are instructed to give briefings about the same subject. These are, or should be, briefings of about 5-10 minutes during the morning Operational Group (similar to a Wing) briefing.

3-What to do in the future?

The present situation is changing in a fast way. In May we received a message from the Operational Command asking for a study to change the regulations about flying and crew rest times. This is the opportunity to begin the study of the medication against crew fatigue and to define the rules about its use during night and sustained operations.

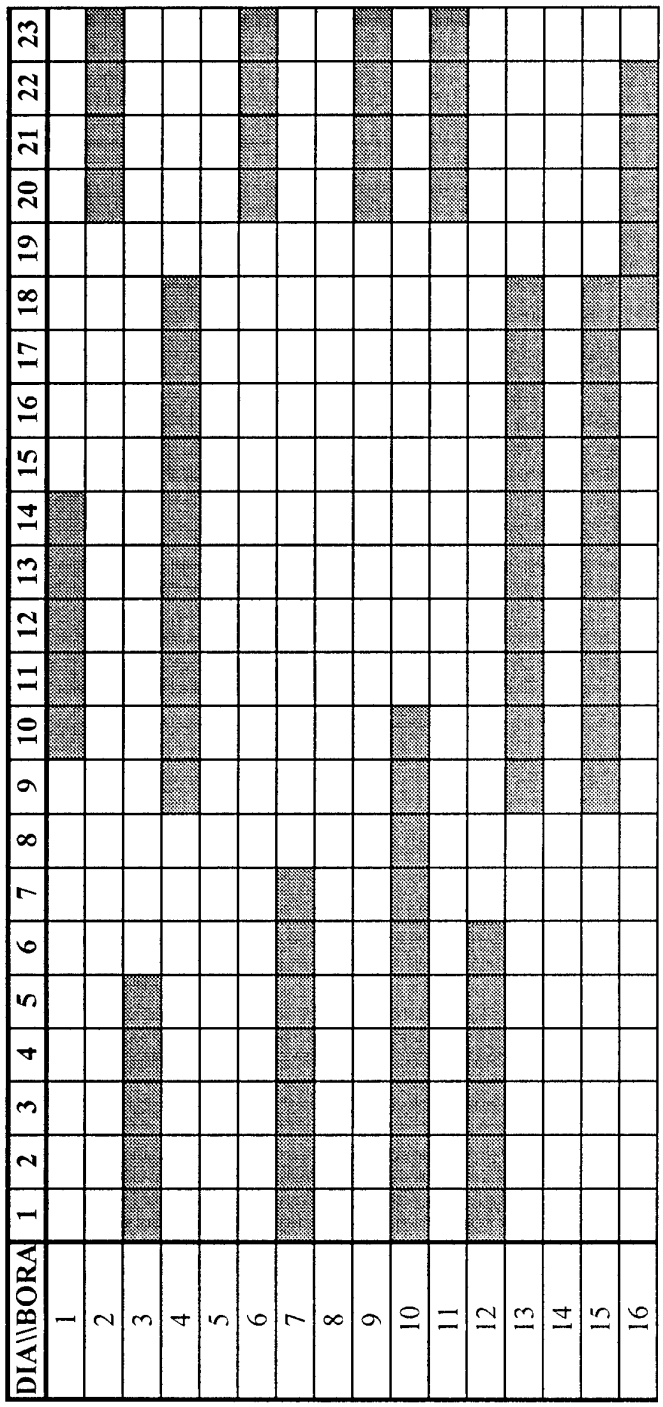
What we intend to do is in first place choose the hypnotic and the stimulant drug to use.

The first approach we did in the Aeromedical Centre is pointing to Zolpidem, like other nations do. About the stimulant we didn't decide what to do.

We will have available, this year, in Portugal the Modafinil. According the research we made in our Centre, probably this will be the drug of choice.

This project will probably start this year.

Figure 1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INDIVIDUAL DIFFERENCES IN REACTIONS TO IRREGULAR WORK HOURS

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Introduction

Irregular work hours cause disturbed sleep, reduced alertness and an increased risk of errors and accidents (Åkerstedt, 1998). The reasons are mainly the circadian system which increases metabolism during daytime and reduces it during night time, thus laying the foundation for effective performance during daytime, but also causing poor sleep during that period (Åkerstedt, 1995). During the night time the circadian nadir instead promotes sleep and causes reduced alertness and performance in the night working individual. The night time effects are also strongly enhanced by the increased time awake preceding the night work period.

However, the effects of irregular work hours clearly differ between individuals - some will have major problems whereas others may thrive on it (Härmä, 1993). Clearly, there is a practical and theoretical interest in trying to understand which individual factors may be of importance in this respect. The present paper will look at some of those factors.

Before starting, however, it should be pointed out that authors have taken very different attitudes to the dependent variable. Thus, outright disease, attitude to work hours, fatigue, sleep disturbance, accidents and performance failure have been used. This has probably contributed to some of the confusion in the area. The variables that have received most attention over the years are age, gender, experience, diurnal type, sleep flexibility, circadian amplitude, and neuroticism. None of them have proved very successful, however, and there might be alternatives. First, lets look at a methodological problem and then discuss the traditional factors.

Most of the studies in this area have been carried out with cross-sectional approaches. Thus, it is very easy to fall prey to circular reasoning. For example if one asks shift works if they have any problems displacing sleep and then asks them what their sleep is like on different shifts, it would be very surprising indeed if one did not find that sleep flexibility is a good "predictor" of sleep disturbances and other problems in shift workers. We run the same risk with neuroticism (it my easily be a consequence of shift work rather than the reverse).

Traditional factors of doubtful value

Neuroticism

One of the most well researched factors is neuroticism. A number of studies have shown consistent high relations with problems in shift work (Parkes, 1994; Iskra-Golec et. al., 1995; Taylor et. al., 1997) On the other hand, one of the few prospective studies show no such relation (Kaliterna et. al., 1995). Obviously, one may suspect that neuroticism may be a consequence of shift work, rather than the reverse (Bohle and Tilley, 1989). This is the prevailing opinion among researchers in this area.

Sleep flexibility

Rigidity of sleep patterns, i.e. feeling unable to move sleep to other times of day than the

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conventional night hours (Folkard et. al., 1979; Costa et. al., 1989), is another dimension that has been used to predict adjustment to shift work in general although little data seem available on its application to alertness patterns specifically. Wynn et al (1986), however found that rigidity predicted general fatigue and sleep difficulties in nurses changing to an alternating day/night work period. However, two prospective studies have failed to find any predictive power. (Vidacek et. al., 1987; Kaliterna et. al., 1995). The results indicate that sleep flexibility is not a factor in tolerance of shift work.

Circadian amplitude

Several studies have tested the hypothesis that the circadian amplitude (usually of the body temperature rhythm) should be related to difficulties in shift work (Reinberg et. al., 1978; Reinberg et. al., 1984). The rational has been that a large amplitude should be more difficult to adjust to phase shifts of work and sleep .However, this does not appear to be the case, most of the amplitude differences between individuals seem to be effects of masking by shift work (Minors and Waterhouse, 1983; Vidacek et. al., 1987).

Gender

Studies of males and females seem to suggest that women should have slightly more problems in shift work, particularly with respect to fatigue and injuries (Novak et. al., 1990; Dirkx, 1991, Oginska, 1993 #2525). And women seem to a slightly larger need for sleep (Wever, 1979). On the other hand, studies which control for responsibility for small children find no differences (Estryn-Behar et. al., 1978, Beermann, 1995 #3401; Estryn-Behar et. al., 1990). And indeed, lab studies of night work show no differences between men and women (Hakola et. al., 1996) . The conclusion seems to be that there is no difference in shift work tolerance between men and women if social responsibility is controlled for.

Traditional factors of possible value

Age

Thus, one might expect age to have a negative influences on sleepiness. This is not necessarily always the case, however, rather the reverse. Several studies suggest that older individuals suffer less from night shift sleepiness than young (Fröberg et. al., 1972; Bonnet and Rosa, 1987; Monk et. al., 1992) . It seems, however, that several night shifts in a row raises sleepiness more in older workers (Härmä, 1995).

With respect to disturbed sleep, there is usually seen an increase with increasing age and experience (Foret et. al., 1981; Åkerstedt and Torsvall, 1981a; Parkes, 1994). In EEG studies we have found trends towards more superficial sleep in middle-aged shift workers (Torsvall et. al., 1981). On the other hand older individuals usually have less problems in relation to early morning work. We have not, however, found any relation between age and sleepiness, except for the fact that accident rates on the road seem to be lower at night in older individuals.

Experience of night work

The two previous studies (Foret et. al., 1981; Åkerstedt and Torsvall, 1981a) also indicated that experience was negatively related to general wellbeing over a number of years. Koller et al (1983) found that reduced health appeared earlier in shift workers than in day workers. Dahlgren (1981) found no effects of three years of night work on the rhythm of rated activation across night shifts. Neither did Wynn (1986) over a temporary 10-week period of weekly alternation between night and day work in a group of nurses. Dumont (1987) found that the amount of sleep/wake and related disturbances in present-day workers were positively related to their previous experience of night work. Guilleminault et al (1982) found an overrepresentation of former shift workers with different clinical sleep/wake disturbances appearing at a sleep clinic.

Neither Folkard et al (1978) nor Knauth et al (1981) observed any such "long-term" adjustment. Van Loon (1963) did claim that one of his three subjects increased his speed of adjustment and Dahlgren (1981) did find that after 3 years of rotating shiftwork the flattening occurred earlier in the week. It is not clear, however, whether this was due to a permanent adjustment, i.e. one that included days off. The data cited, together with the increased subjective nightshift difficulties which have been found to be associated with increasing age and experience (Foret et. al., 1981; Torsvall et. al., 1981; Åkerstedt and Torsvall, 1981a) do not speak strongly for experience as a major factor in adjustment. The issue, however, can only be answered definitely through a longitudinal study.

In relation to shift work there is some indication that morningness is associated with poor adjustment to shift work (Aanonsen, 1964; Folkard et. al., 1979; Åkerstedt and Torsvall, 1981b). Breithaupt (1978) and Härmä (1995) failed to find such a relation and prospective studies (Kaliterna et. al., 1993; Vidacek et. al., 1993; Kaliterna et. al., 1995) found no predictive power. Frequently it is found that morningness and age are highly correlated and that the any "effects" of diurnal type may rather be effects of age. An additional observation is that there is a selection into shift work of evening types (Knutsson and Åkerstedt, 1992). We also found in an early study that three-shift workers who were transferred to day work (for organizational/economical reasons) change their diurnal type strongly towards morningness (Torsvall and Åkerstedt, 1980).

Physical condition

Possibly, also the physical condition of the individual might be of importance to night shift sleepiness. Thus Härme et al (1986) had three-shift workers improve their physical fitness through a training program. This greatly reduced rated overall fatigue as well as increased two-hourly ratings of alertness on the night shift. Another factor that will exacerbate night work sleepiness is sleep pathology such as that associated with, for example, sleep apnea (Lavie, 1981)

Some alternative possibilities

As indicated above there are available very few experimental or prospective studies that may shed light on the inter-individual differences in tolerance of night work. However, we have conducted several studies that may be of some interest in this context.

Individual differences in tolerance in rapidly rotating shift work

One approach to inter-individual differences in tolerance may be to compare tolerants and non-tolerants on a number of trait and state variables. We used this approach in a 400 rapidly rotating shift workers at a paper mill (Åkerstedt, unpublished data). The schedule involved a Night shift (2200h-0600h) - 8 hours off - an Afternoon shift (1400h-2200h) - 8 hours off - a Morning shift (0600h-1400h) - 56 hours off (i.e. 2 normal night sleeps). Then the cycle repeated again six more times, after which followed a week off.

From the total population was selected a group of 60 subjects who scored 1 or 2 (very negative + negative) and 4 or 5 (positive + very positive) on the scale describing their attitude to their work hours. Half the subjects in each group were women. The four resulting groups were also followed with actigraphy, sleep diaries and daily alertness logs during triad 1, 3 and 5. The results were analyzed using a two-factor ANOVA with gender and attitude as factors.

The results showed that among the factors that did not differentiate between the attitude groups or showed an interaction, were age, BMI (significant effect for gender), marriage status, number of children, or diurnal type. However the non-tolerants reported significantly more sleepiness, less "sufficient sleep", less feeling well restide, a higher need for sleep (8.31±.31h vs 7.15±.21 for men and 8.83±.47 vs 8.23±.31h for women) - note that women reported a significantly

higher need for sleep. In addition, testosterone levels were lower in non-tolerants (9.4±.9 vs 13.5±.1 nmol/L), whereas prolactine and cortisol did not differ. Three more variables became highly significant and were the ones entering the final step of the stepwise multiple regression analysis (in which all previous variables were tested) against attitude. This were Mean Sleepiness during the afternoon shift (R2=.37, beta=-.62), Sufficient time for family (R2=.17, beta=.57) and Sleep quality before the night shift (R2=.09, beta=.48). Note that the sleepiness on the afternoon shift would be high if sleep after the night shift was unsuccessful. The results clearly suggest that the important factor behind the attitude were related to sleep and sleepiness in relation to the displaced work hours, and to the social consequences.

Differences in tolerance of long shifts

In another study we tried to find what was related to tolerance of a schedule which required seven 12h shifts (0700-1900h) followed by a week off (Åkerstedt, unpublished data) Here we selected one extreme group (12 workers) who reported no fatigue during the working week and another who reported fatigue, although rather moderate. Both groups were strongly in favor of their schedule because of the week off. The same measurements were used as in the previous study.

The results showed that the fatigued group reported lower sleep quality and shorter sleep (5.4±.2 vs 6.0±.2h), longer time awake, higher sleepiness during the working week. During the recovery week they slept longer (8.9±.3 vs 7.9±.3). They were also more morning oriented and younger.

When these variables were tried in a stepwise multiple regression analysis against fatigue it was found that the only significant predictor became "Well rested" (R2=.34, beta=-.58). To study the dynamics this variable was removed and the new significant predictor became "Sufficient sleep" (R2=.33, beta=-.58). When this variable was removed age (low) became the significant predictor (R=.17, beta=.41), and when age was removed, both diurnal type (evening) and need for sleep (high) became significant (R=.17, beta=.42 and R2=.17, beta=-.41). TST, Sleep efficiency, Sleep quality, Ease of rising, Number of small children, etc remained outside of the regression. The results suggest, again, that sleep and alertness are key factors, but here it also seems that some of role of sleep and alertness is related to age, diurnal type, and need for sleep. Note that the group studied were day workers who had to rise from sleep around 6 a.m. This may have brought in diurnal type and age.

Conclusion

This limited review suggests that some traditional factors like, personality and circadian amplitude seem to have little to do with tolerance of shift work. Neither does gender, at least not if social responsibility is controlled for. Age on the other hand seems of more interest and also diurnal type, but the two seem closely related.

However, the major determinants of shift work tolerance probably have more to do with states or rather ways of coping with irregular work hours. Thus, the way an individual organizes his behavior to promote sleep may be of importance, as may be the need for sleep. This may be related to commitment to night work, avoiding light after night work, etc. One should probably give priority to teaching sleep/wake optimization, rather than trying to find individuals with particular traits. One gets the feeling that the highly tolerant single night shift worker would be older, have a low need for sleep, have a high sleep quality, be in good physical shape, and plan sleep strategically (using naps). If several night shifts occur in sequence, younger individuals may have an advantage.

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SLEEP TENDENCY AND ABILITY TO SUSTAIN WAKEFULNESS

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INTRODUCTION

During sustained military operations it is often necessary to cope with prolonged periods of wakefulness and irregular rest-activity patterns. In these situations a severe sleep debt can accumulate, leading to increasing levels of sleepiness on the job and, consequently, to dangerous decreases of performance. A number of possible pharmacological and non-pharmacological countermeasures have been studied. Prophylactic naps (short periods of sleep before long periods of work) are probably the best non-pharmacological tool to reduce fatigue and improve performance (e.g., Bonnet, 1991). They have to take place according to some "chronobiological rules": for example, it is well known that sleep propensity shows a biphasic distribution, with an early morning (5.30-7.30 hours) and a mid afternoon (15.30) peak, defined "primary and secondary sleep gates" by Lavie (1986). In addition, naps should be scheduled before the accumulation of a severe sleep debt and placed far from the circadian through of body temperature rhythm, in order to minimize sleep inertia effects (e.g., Dinges, Orne, Orne, 1985).

When operational conditions are characterized by environmental and psychological factors that do not permit to have useful naps, drugs such as benzodiazepines can be used to both induce and maintain sleep (Nicholson, Stone, Pascoe, 1980; Nicholson, Stone, 1986); other drugs (caffeine, amphetamines, modafinil) have been successfully used to sustain wakefulness (e.g., Johnson, Freeman, Spinweber, Gomez, 1991; Pigeau, Angus, 1997).

However, up to now a poor attention has been payed to the individual differences in adaptability to unusual sleep-wake cycles. Individual differences should be carefully taken into account when selecting personnel to be involved in sustained operations and irregular rest-activity schedules. For example, it is well known that evening-type people can more easily adapt to work at night and to sleep during the day than morning-type people (e.g., Breithaupt, 1978). In addition, in the course of prolonged and intensive operations, it is not easy to exactly schedule periods of sleep. In other words people can be required to sleep at unusual hours or "forbidden zones for sleep", and to work during "forbidden zones for wake" (e.g., Walsh, Tepas, Moss, 1981). For these reasons, in applicative contexts can be very relevant to select personnel characterized by both high *sleepability* (the ability to sleep whenever it is permitted) and high *wakeability* (the ability to sustain wakefulness for long periods of time).

A number of tools are available to quantify sleep propensity and/or ability to remain awake during irregular work hours. Objective evaluation of *sleepability* can be obtained by means of the Multiple Sleep Latency Test (-MSLT- Richardson, Carskadon, Flagg, Van den Hoed, Dement, Mitler, 1978). MSLT is based on the idea that drowsiness is close to readiness to fall asleep: in fact subjects are required to lie down in bed and to attempt to fall asleep for several times (4 to 6) during the day, while being polygraphically monitored (EEG, EOG, EMG). The mean duration of sleep latency is considered as measure of sleepiness: the shorter the sleep latency, the higher the sleepiness.

On the other side the *wakeability* is usually assessed with Maintenance of Wakefulness Test (-MWT- Mitler, Gujavarty, Browman, 1982), a variant of the MSLT that requires the subjects to sit in a comfortable, high-backed chair, with their eyes closed, in a darkened room with instruction to "remain awake". The criteria to assess

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sleepiness are the same used in the MSLT procedure.
MSLT and MWT constitute an assessment of distinct aspects of the sleepiness/alertness dimension, as shown by studies on shift workers and sleep apnea or narcoleptic patients (Sangal, Thomas, Mitler, 1992; Sugerman, Walsh, 1989).
In the present study sleepiness and alertness were objectively measured, by means respectively of MSLT and MWT, during the night after a daytime administration 20 mg of Temazepam (TMZ) in soft gelatine capsules or placebo (PLC) to obtain a prophylactic sleep. Furthermore, we here report two "single-case" studies on military pilots complaining of excessive daytime sleepiness.

MATERIALS AND METHODS

Subjects

Eight males (mean age= 33.5 ± 9.4) with no sleep, medical, or psychiatric disorders participated as volunteers in the study. All of the subjects reported a normal rest-activity cycle - with monophasic sleep from 23.00 to 7.00 ± 1 hour - and all of them were drug free.

Polygraphic measures of sleepiness/alertness

During both MSLT and MWT trials, EEG was recorded from four monopolar locations (C3-A2, C4-A1, O1-A2, O2-A1); EOG was recorded from the left and right outer canthus, both referred to FPz. Submental electrodes were employed for recording bipolar EMG. The impedance between electrodes was kept below 10 Kohms. All recordings were in AC. For data collection, a polygraph "VEGA 24" (OTE BIOMEDICA) was used, with a paper speed of 10 mm/sec. Sleep stages were scored according to international standard criteria (Rechtschaffen & Kales, 1968).
Multiple Sleep Latency Test (MSLT). Sleep latencies were recorded in a dark, sound-proof room, with subjects lying in bed attempting to fall asleep, using standard procedure (Carskadon, Dement, Mitler, Roth, Westbrook, Keenan, 1986). Subjects were awoken immediately after two consecutive 30 sec epochs of any stage of sleep, and the score was taken as latency to the first epoch of any stage of sleep. If sleep onset did not occur, a latency of 20 min (the end of the test) was used for data analysis.

Maintenance of Wakefulness Test (MWT). The MWT (Mitler et al., 1982) required the subjects to sit in a comfortable, high-back chair, with their eyes closed, in a darkened room with the instruction "to remain awake". Sleep onset definition and termination criteria were the same used as in the MSLT procedure.

Procedure

The experimental design was based on a double-blind, balanced administration of 20 mg TMZ in soft gelatine capsule or PLC before a daytime sleep. The two conditions (TMZ vs PLC) occured on two non-consecutive days separated by at least 1 week. On each experimental day subjects slept in the laboratory, after the assignment to TMZ or PLC (lights out at 14.30 ± 30 minutes until maximum 22.00).
During the night, starting from 23.00, the subjects underwent four consecutive testing sessions (each one comprising several psychophysiological and paper and pencil tasks assessing attentional performance). The MWT trials were done at the following times: 23.30, 1.30, 3.30, 5.30, while the MSLT trials at 0.30, 2.30, 4.30, 6.30.

Data analysis

Sleep latencies on MWT and MSLT were submitted to a repeated measures ANOVA *Test* (MWT, MSLT) x *Condition* (TMZ, PLC) x *Session* (1,2,3,4) was performed. Trend analysis was used to evaluate time-of-day effects. Duncan test was used for *post hoc* comparisons of the means.

Single-case studies

Two military pilots (P.R. and A.C.), aged respectively 29 and 41 years, complaining of excessive daytime sleepiness, were submitted to four MWT and MSLT sessions during the day, with the following schedule: MWT trials at 11.00, 13.00, 15.00, 17.00; MSLT trials at 11.30, 13.30, 15.30, 17.30.

RESULTS

ANOVA showed a significant effect for *Test* ($F_{1,7}=31.02$; $p=.001$), with shorter mean latencies on MSLT (6.48 min) than on MWT (15.98 min) and for *Session* ($F_{3,21}=12.8$; $p=.0001$), but no effect for *Condition* ($F_{1,7}<1$).

A significant interaction *Test x Session* ($F_{3,21}$=9.0; p<.0005) was present, with trend analysis showing a significant linear trend during the night only for MSLT ($F_{1,7}$= 23.83; p=.002, see Figure 1).
Moreover a significant interaction *Test* x *Condition* ($F_{1,7}$=8.14; p=.02, see Figure 2) was found, with higher latencies on MWT in the TMZ condition (Duncan test: p<.05). Finally, *Test* x *Condition* x *Session* ($F_{3,21}$<1) interaction was not significant. In the table 1 are reported means (± SD) of sleep latencies (in minutes) on MWT and MSLT in the 4 nocturnal sessions of the two conditions.

Table 1. Means (± SD) of sleep latencies (in minutes) on MWT and MSLT in the 4 nocturnal sessions of the PC and TMZ conditions.

Variables	**Nocturnal sessions Post-PLC**				**Nocturnal sessions Post-TMZ**			
	SES 1	SES 2	SES 3	SES 4	SES 1	SES 2	SES 3	SES 4
MWT	16.5	15.87	15.69	12.23	18.36	18.86	14.71	15.31
(Sleep latencies)	(6.48)	(7.65)	(7.46)	(7.96)	(4.02)	(2.10)	(6.49)	(5.93)
MSLT	11.75	7.87	5.75	3.44	8.68	7.44	3.12	3.81
(Sleep latencies)	(4.42)	(7.73)	(7.31)	(4.30)	(5.67)	(4.68)	(1.75)	(3.83)

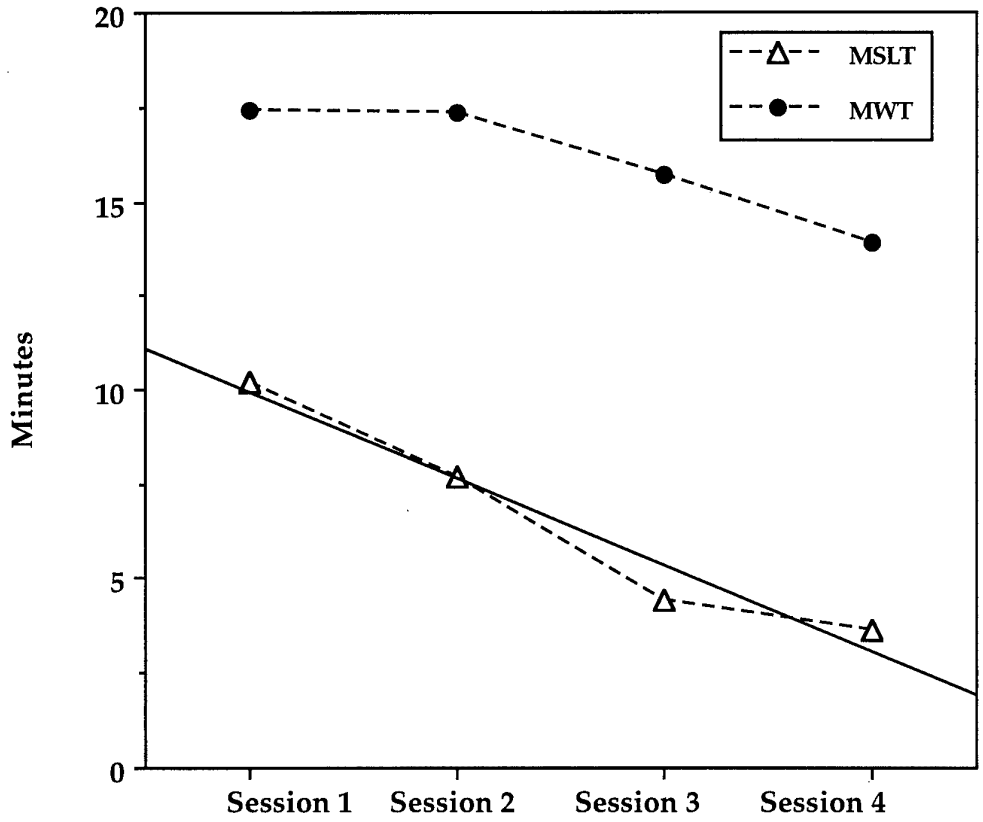

Figure 1. Mean sleep latencies on MWT and MSLT during the four nocturnal sessions. Significant linear trend for time of day effect is indicated by interpolate curve.

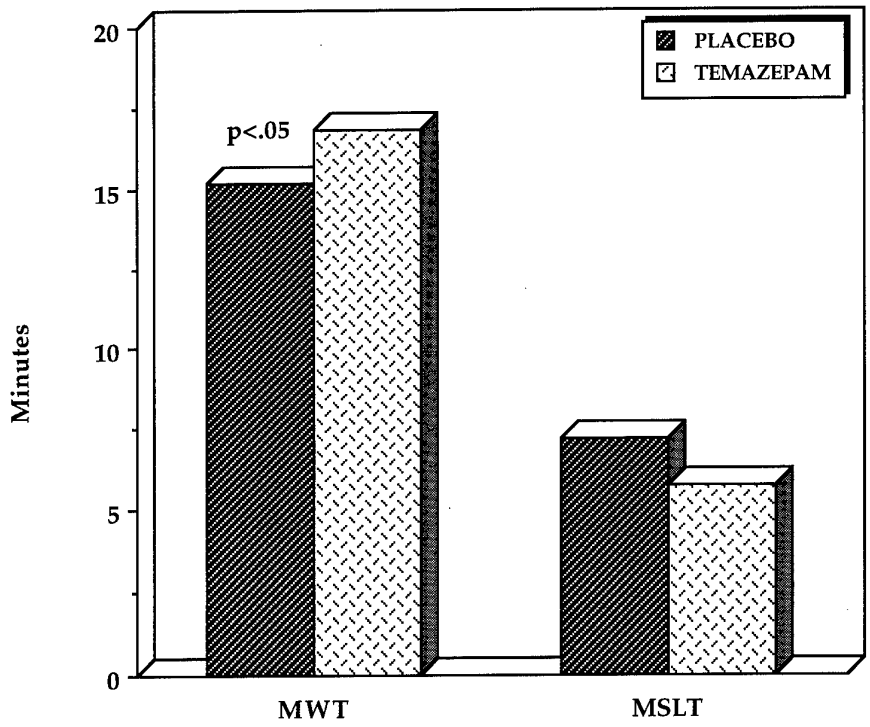

Figure 2. Mean sleep latencies on MWT and MSLT during the night, after diurnal sleep with TMZ or PLC.

With regard to the two single-case studies, the visual inspection of plotted MSLT and MWT latencies (see figures 3 and 4) seems to reveal different patterns of dissociation between *sleepability* and *wakeability*. Subject A.C. showed a high ability to maintain wakefulness during the day never falling asleep at MWT trials, in spite of very short sleep latencies (<5 min) in the first 3 MSLT trials. On the other hand, subject P.R. always showed sleep latencies in the pathological range, except than during the first MWT trial.

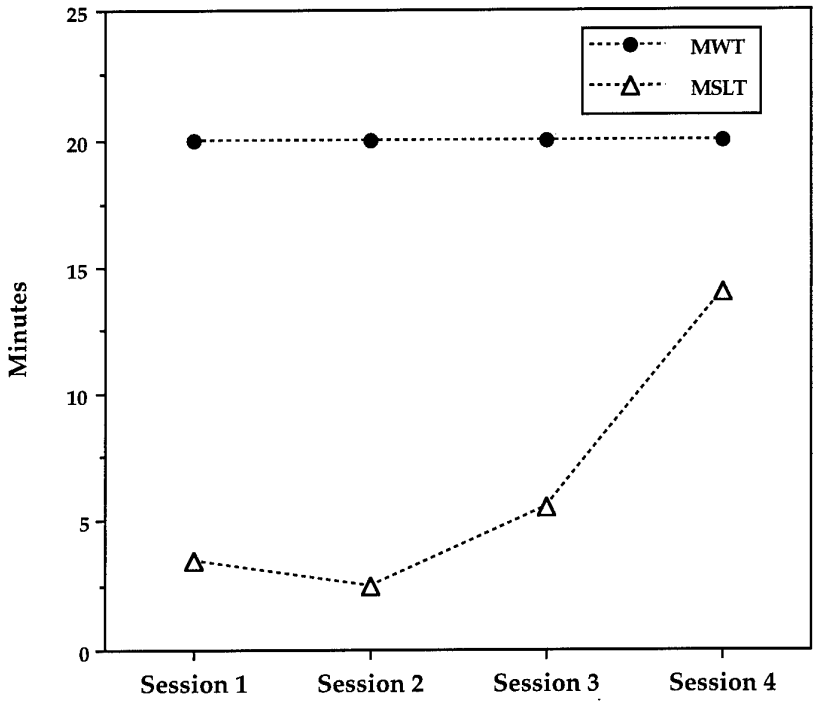

Figure 3. Mean sleep latencies on MWT and MSLT during the day of a military pilot complaining of excessive daytime sleepiness (subject A.C.).

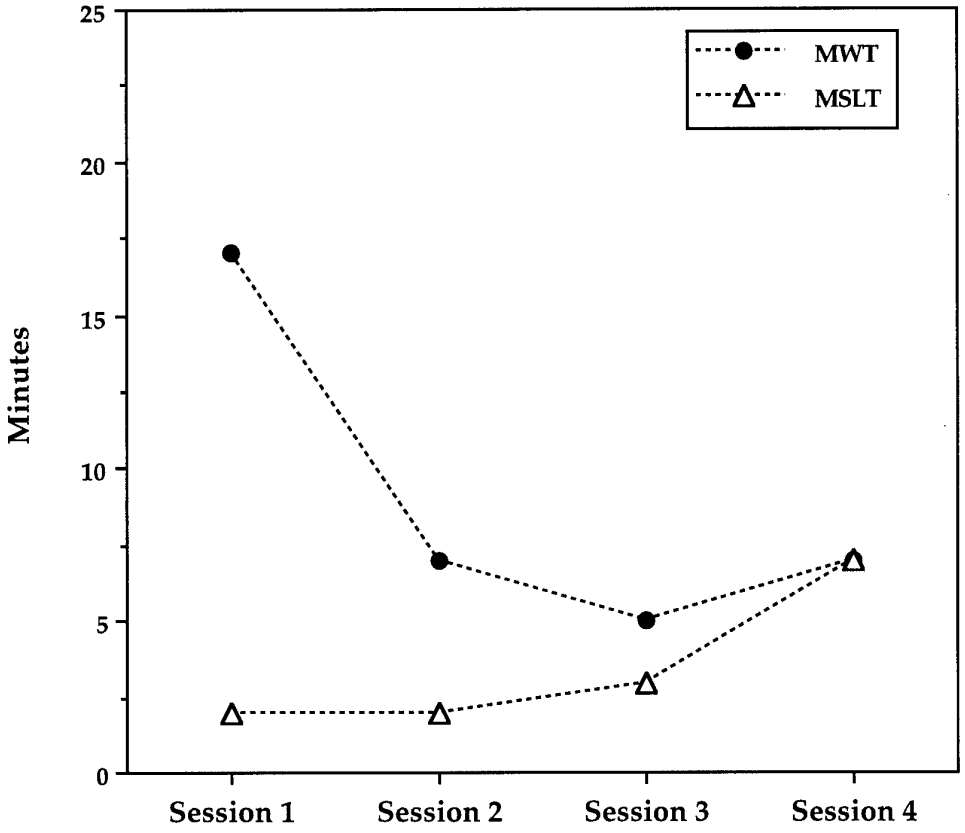

Figure 4. Mean sleep latencies on MWT and MSLT during the day of a military pilot complaining of excessive daytime sleepiness (subject P.R.).

DISCUSSION

Our results confirm that MSLT and MWT constitute assessment of distinct aspects of the sleepiness/alertness dimension (e.g., Porcù, Bellatreccia, Casagrande, Ferrara, Tricarico, 1996). In fact, the ability to stay awake - measured by MWT- was not substantially affected by circadian factors, remaining stable during the night. The circadian trend of sleepiness is better revealed by MSLT, that showed a linear increase of sleep propensity during the night (decreasing sleep latencies on MSLT).

The effect of instructions is confirmed also during the acute night shift following diurnal sleep, being the MSLT sleep latencies significantly shorter than the MWT ones.

In addition, we found higher latencies on MWT in the TMZ condition as compared to the PLC condition; in other words, the assumption of temazepam prior to daytime sleep positively affected the ability to remain awake during the following night. On the contrary, sleep propensity, as reflected by MSLT latencies, was not affected by the lengthening of diurnal sleep after TMZ intake.

Both findings - time-of-day and drug effects - confirm that MWT and MSLT imply different physiological processes, namely *sleepability* and *wakeability*. Such a dissociation between *sleepability* and *wakeability* is also confirmed by the single-case studies here reported. Results regarding subject A.C. clearly indicate that a high ability to maintain wakefulness when requested can coexist with a very high level of daytime sleepiness, as expressed by very short sleep latencies at MSLT (<5 min, in the range of pathology).

Harrison and Horne (1996) recently interpreted the high *sleepability* found in some healthy subjects (short MSLT latencies during the day)

as a simple ability to relax and 'switch off' very efficiently. These subjects seem to be pathologically sleepy, but they do not show any other symptom of excessive daytime sleepiness, are good sleepers, and do not complain of excessive daytime sleepiness. This ability seems to be a relatively stable individual trait in sleep propensity, as Harrison and Horne's subjects showed no improvement to MSLT latencies even under ad libitum sleep conditions.

In conclusion, our results suggest the usefulness to assess *sleepability* and *wakeability* in the selection of personnel eventually required to cope with sustained operations during the night and/or with prolonged irregular rest-activity patterns. .In fact, whenever an abrupt shift of the sleep-wake cycle is required - such as during emergencies, military operations, trans-meridian travels or shift-work - the need to sleep and to properly perform at unusual hours with respect to the underlying circadian rhythm usually leads to cumulative sleep curtailment and decrements of performance (e.g., Tilley, Wilkinson, Warren, Watson, Drud, 1982). In such situations, people that can easily go to sleep in the daytime and sustain wakefulness for long periods of time should be preferably selected.

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USEFULNESS OF SLEEP RECORDS AFTER MILD HEAD TRAUMA TO PREDICT SHIFT WORK EFFECTIVENESS

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Summary

Validity of polysomnography for determining the post-traumatic sequelae was evaluated in 33 male patients after a mild head trauma. The results indicate that shortly after the trauma accompanied by the brain commotion disturbances in sleep architecture can be detected by means of polysomnography. We also demonstrate that polysomnography is a sensitive method of evaluation of early post-traumatic alterations within the CNS. Based on the results of the present study we conclude that the described diagnostic procedure should become a steady element of the clinical evaluation and qualification of patients presenting with subjective symptoms as the sequalae of a mild head trauma.

Introduction

Minor head trauma (MHT) accompanied by brain concussions constitutes, as a clinical syndrome, about 2/3 of all the scull and brain injuries [8]. Most of the patients with the past history of the MHT recover within a few weeks without a need for a specific intervention. A third of the patients, however, develop the subjective, post-traumatic syndrome, and half of them never return to work. One year after the injury, 15% of the patients still complain of symptoms affecting their lifestyle [1]. Probably the pathological process developing after trauma could be considered the reason of complaints of sleep disturbances too. Therefore authors suspect that in early period after MHT patient can develop disturbances in sleep. We did not find any research work analizing a sleep pattern in a group of patients in early period after MHT.

The present paper is a part of the research project carried out at the Polish Air Force Institute of Medicine (PAFIM), the Central Clinical Hospital of the Military Medical University School (CCH) and the Institute of Psychiatry and Neurology (IPN) in Warsaw. The project was devoted to evaluation of the state of the central nervous system in patients who had suffered from MHT. Here, we evaluated the sleep pattern of patients in early period after MHT.

Material

The study was conducted in a group of 40 males aged 19-29 years (mean age 22.5 y) who were admitted to the Dept. of Neurology, PAFIM for the MHT accompanied by the consecutive brain concussion. The diagnosis was based on history, physical examination, and the computerized tomography (CT) results. The protocol of the study was approved by the Ethical Committees of both the PAFIM and the CCH and a written consent was obtained from all the subjects allotted to the study.

Selection of the patients for the study was based on the following criteria: skull and brain injuries with brain commotion experienced for the first time shortly before the study (i.e., 24 - 96 hours before hospitalisation), 19-41 years of age, male sex, and no detectable mental disorders, somatic diseases or other physical abnormalities. In addition, no past history of abnormal EEG recordings and no family history of epilepsy were required.

Seven patients should take medication and were excluded from the survey (two of them because of excessive emotional irritability, one because of serious dizziness and three because of persisted moderate and heavy headache).

Control group consisted of 30 healthy paid male volunteers aged 19-29 years (mean age 22.4y) with normal EEG in wakefulness. All examined persons described their sleep as good. None of them abused alcohol, took daytime naps, or underwent pharmacological treatment for at least four weeks before the sleep examination.

Method.

After admission to the Clinic patients were assessed from the point of view of cause of trauma,

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duration of unconsciousness, appearance and duration of posttraumatic amnesia (PTA).

The injuries were evaluated using the Glasgow Coma Scale (GCS). Accordingly, the total score (ranging from 3 points for the most serious condition to 15 points for the least serious one) obtained after the assessment of the eye-opening capacity and the verbal and motor responses was used to divide the patients into the following 3 groups: a) mild (scaled 13-15), b) moderate (scaled 8-12), and c) heavy head trauma (scaled 3- 7).

During the first 24 hours after the admission, the brain CT with no contrasting medium was performed. Normal images of the brain and the cerebellum with no detectable dislocations in the ventricular system were required for the inclusion of a patient in the study. All the CT images were examined by one and the same physician.

On 3rd to 4th day after trauma, by means of "self-estimation sleep form" patients described their wake/sleep status, replying to 12 questions connected with the pattern of sleep after trauma, day sleepiness and naps. They compared it with the quality of sleep before MHT.

On the 5th to 11th day after the trauma, polygraphic examinations were carried out on the Medelec-2 MC apparatus between 9.00-10.00 p.m. and 5.00-6.00 a.m. Standard technique polygraphic record and the criteria of visual scoring of somnogram stages according to Rechtsschaffen and Kales [2,14] were applied. Sleep was evaluated on the basis of the somnogram of the second night (the first night was considered as adaptation night). The same procedure of sleep examination was applied in control group after a normal activity during a week before the examination.

The data concerning sleep EEG were computer processed, mean values and standards deviations for 17 parameters were calculated. Students t-test was used for the statistical analysis of the results. $P<0.01$ was adopted as significant difference.

Results

Patient's characteristics

According to history data 18 patients (54.5%) suffered injury from fights, nine (27.3%) from car accidents and six (18.2%) from fall. Eleven of them (33.3%) were only confused or lost consciousness for less than dozen or so seconds. Twelve patients (36.4%) lost consciousness for 1 to 20 minutes and ten patients lost consciousness for 30 to 60 minutes.

Retrograde amnesia (RA) occurred in every patient and lasted up to a few minutes after trauma. Posttraumatic amnesia (PTA) appeared in every patient as well, but the time of duration was up to 6 hours. Data concerning RA and PTA have only approximate value, because in 27 cases memory improved before admission to the hospital.

On the admission to the Clinic (first-third day after the trauma) the patients complained of a number of symptoms which disappeared after a few days. The complaints included headaches, dizziness, daytime drowsiness, nausea, and emesis. Headaches of mild and moderate intensity (not requiring any regular medication) as well as irritation and anxiety episodes were the longest lasting symptoms (6 subjects (18.2%) complained of them for 14 days after the trauma).

According to the CGS, 25 (75.8%) patients were scored 15 points and 8 (24.2%) patients were scored 14 points. In the latter group, one point was subtracted from the highest score because the patients were able to open their eyes on demand.

Self-estimation sleep form.

All patients had no sleep disturbances and even naps before head trauma. According to the form results (table I) 22 subjects had different sleep abnormalities day sleepiness and naps after MHT. Five of them (gray mark on the table) had excessive sleep disturbances and woke up with the feeling of fatigue.

Polysomnography

Results of patients' sleep examinations are shown in the table II. They are compared with the results of control group. Statistical analysis revealed a reduction of sleep cycle length ($p=0.001$) in patients. However an increase of cycle number ($p=0.009$) during a whole sleep period in subjects after MHT, caused that total amount of NREM sleep is similar in both groups. Another difference found in NREM sleep between two groups is decrease of stage 2 of sleep in patients ($p=01$). Analysing REM stage we observed shortening of REM sleep latency ($p=0.0001$).

Polygrafic registration of sleep in patients took place between 4 to 11 days after trauma. In 19 of them from 4^{th} to 6^{th} day and in 14 from 8^{th} to 11^{th} day after MHT. Statistical analysis showed no difference between two estimated groups.

As it is demonstrated in table I patients had some complaints connected with disturbances in wake – sleep cycle. Significant sleep differences were found in group of patients who, apart from other complaints, notified feeling of fatigue. However because of a small number of this group we should be careful in making a conclusion.

Discussion

Traumatic injury is mainly caused by displacement of intracranial structures in relation to the skull bones. A shift of these structures towards the trauma site creates a negative pressure which results in the formation of a vacuum on the opposite side of the brain. The vacuum sucks in gas bubbles to the cerebral cortex capillaries and breaks down small blood vessels and nervous tissue (the so-called cavitation phenomenon) [2]. After injury focal and diffuse pathological changes occur. MHT is mainly characterized by diffuse changes like diffuse axonal injury (DAI), diffuse microvascular damage (DMD) and delayed secondary injury (DSI). DSI is caused by an uncontrolled vicious cycle of biochemical events at cellular level set in motion by the trauma. DSI has come to be recognized as a major contributor to the ultimate tissue loss after MHT. The complex of pathological processes lead to necrosis and/or apoptosis of nerve cells [6,9].

Exposure to the linear acceleration forces brings about the most pronounced changes in the deep structures of the brain. Angular acceleration damages mainly the cerebral cortex of, particularly frontal and temporal lobes. - in which centres responsible for human behaviour, memory, cognitive and learning ability are found [18]. Experimental research works revealed that some cerebral structures, located in frontal and temporal lobes as well, are involved in creation of final sleep-wake status picture [10]. Thus behavioral and cognitive abnormalities are often found in patients with MHT.

History of sleep disorders is one of factors affecting a quality of shift work. Traumatic brain injury can affect even temporary, activity of systems responsible for wake-sleep cycle. EEG sleep pattern of comatose patients after head trauma was the evidence of changed function of those systems [8]. Prigantano at al. [12] obtained single polysomnograms in a group of 10 subjects who had complains of disturbed sleep after closed injury. All of these patients had been comatose for at least 24 hours. The head-injured patients had less stage 1 sleep and a greater number of awakenings.

This research work has revealed that even after MHT, in early period after trauma, changes of sleep architecture can be observed. Decrease of stage 2 sleep is difficult to explain. It could be the result of affected function of structures (located in frontal and temporal lobes) involved in NREM sleep generating. In patients with diagnosed Alzheimer Disease (AD) pathological changes are especially found in frontal and temporal lobes. EEG sleep pattern of these patients disclosed poor biological efficiency and disturbances of REM stage [17].

Domżal et al. [3] discovered in their study that patients after MHT had a decrease of spindles activity – EEG elements found in NREM sleep pattern. Diminishing of spindle number results in reduction of stage 2 sleep. System consisting of reticular formation, thalamus and cerebral cortex is responsible for creation of spindles [11,13,16]. That is why affection of connections between these structures is thought as essential factor causing decrease of stage2 sleep.

REM stage changes found in examined group may depend on affected function of centres located in cerebral hemispheres. Neurons generating REM stage are found in structures of brain stem but different cerebral nuclei influence on the final shape of this part of sleep [4,5,15,19].

REM sleep is thought to be responsible for brain metabolic regeneration [7]. Shortening of REM stage latency, duration of sleep cycle, and increase of cycle number could be the result of acceleration of the process.

Conclusions:

1. MHT affects a sleep architecture in early period after trauma.
2. Polysomnography is a sensitive tool in discovering of sleep changes developing after MHT. It could help to improve clinical patient estimation and usefulness to perform shift work.

Table I.

Complaints of patients according the „sleep self – estimation form"

Lp.	Number of patient	Complaints				
		Day sleepiness	Naps	Difficulties in falling asleep	Often Awakenings During night	Feeling of fatigue
1.	1	X	X	X		X
2.	2	X				
3.	3	X	X			
4.	6	X				
5.	9	X				
6.	10	X				
7.	11	X	X	X		
8.	12	X		X	X	
9.	13	X	X	X	X	
10.	16	X	X	X	X	
11.	17	X	X			
12.	19	X	X	X	X	
13.	21	X	X	X	X	X
14.	22				X	
15.	25	X	X			
16.	29	X	X			X
17.	30			X	X	X
18.	32	X				
19.	33				X	
20.	34	X	X			X
21.	35	X	X			
22.	36	X	X	X	X	

Table II

EEG sleep pattern of patients after mild head trauma versus control group.

Parameters of EEG sleep pattern	A control group		Patients		Significance of difference
	Mean value	SD	Mean value	SD	
Record time (min)	474.9	8.6	476.3	2.5	p=0.25
Time of sleep (min)	439.1	25.8	433.4	33.1	p=0.45
Total sleep time (min)	433.2	32.5	426.1	33.7	p=0.40
Wakefulness in sleep (%)	1.4	3.0	1.7	2.1	p=0.66
Stage I (%)	6.4	5.9	6.1	3.8	p=0.82
Stage 2 (%)	55.6	7.2	51.3	5.8	p=0.01
Stage 3 (%)	11.0	3.8	11.7	3.1	p=0.42
Stage 4 (%)	4.4	4.1	5.5	4.6	p=0.28
Stage 3+4 (%)	15.4	6.9	17.3	6.0	p=0.25
Total NREM sleep (%)	77.5	4.7	74.8	4.6	p=0.03
Stage REM (%)	22.5	4.7	25.2	4.6	p=0.03
Sleep latency (min)	35.2	24.0	42.8	32.7	p=0.29
Stage 3,4 latency (min)	13.1	5.6	17.3	17.1	p=0.19
REM stage latency (min)	88.9	40.2	54.1	22.7	p=0.0001
Number of sleep cycles	4.0	1.0	4.7	0.8	p=0.009
Number of awakenings	2.0	2.8	2.6	2.4	p=0.37
Mean length of cycle (min)	108.7	23.5	91.5	13.9	p=0.001
Sleep efficiency (%)	91.3	6.3	89.4	7.0	p=0.27
Sleep maintenance (%)	98.6	3.0	98.3	2.2	p=0.67

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Sleepiness in a Population of Italian Shift-work Policemen

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Introduction

Various studies have shown that sleep disorders and daytime sleepiness are the more frequent disturbances reported by shift-workers (1,2). Shift-work interferes with both the quality and quantity of sleep. Concerning the duration of sleep, there is a decrease in the number of hours of sleep both during morning shifts, due to early awakening, and during night shifts due to the inversion of the normal sleep-wake cycle (3). The increase in body temperature, observed starting from the early morning hours, and the unfavorable environmental conditions (noise, family and social life, etc.) make it more difficult to fall asleep during the day (4,5). Data reported in the literature show how sleepiness and fatigue can increase the risk of human errors and accidents (6,7). Night work and loss of sleep may account for some recent serious accidents (Three-Mile Island 1979, Chernobyl 1986, Exxon Valdez 1989).
The consequences of an altered sleep quality, with possible reductions in vigilance levels, seem to be particularly relevant when shift-work is associated with tasks requiring high performance levels and involving stressing working conditions. This situation is constantly present in Police Force personnel, a working group scarcely taken into consideration by international literature (8,9).
The aim of our work has been to evaluate, with an assisted questionnaire, the prevalence of daytime sleepiness and the possible relationship between sleepiness and intrinsic sleep disorders and/or sleep disturbances due to the shift-work condition in the overall population of shift-workers policemen of the town of Genoa.

Subjects

This study covers the period from September 1996 to February 1997. According to the October 1996 census, the city of Genoa has a population of 653,000 inhabitants and is ranked third as to crime rate in Italy (10). The subjects enrolled in this study were informed on the objectives and methods used during the investigation. The investigation was carried out using a self-administered questionnaire; complete confidentiality was guaranteed during data collection and processing. The subjects were also given telephone numbers where they could get information in case of doubts (the physician in charge of the investigation was available), should the wording of any of the questions be unclear or should its meaning be ambiguous.
We have evaluated the questionnaires obtained from 504 male shift-workers (M) and 101 female shift-workers (S), mean age 30 +/- 5 yrs.
The sample of shift-workers included personnel employed in tasks which are generally considered stressful from a psychophysical point of view; such evaluation is based on the content of tasks entailing risks (escort service, patrol service, flying squad, etc.). They were all working fast rotating shifts organized according to the following plan: 1st Evening, 19:00-01:00 h; 2nd Afternoon, 13:00-19:00 h; 3rd Morning, 07:00-13:00 h; 4th Night, 01:00-07:00 h; 5th Rest. Furthermore, special operational

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requirements could entail an extension of the working period without an immediate recovery.

Questionnaire

The identification of subjects with pathological sleepiness was assessed using a subjective evaluation scale (Epworth Sleepiness Scale, ESS, Murray WJ 1991) (11) translated into Italian by the authors. The scale measures the tendency to sleep in different daily life situations. It has been validated in normal subjects and in patients suffering from different diseases leading to daytime sleepiness and has shown good discriminating sensitivity and excellent correlation with the results obtained with objective neurophysiological procedures (12).
In a second step, in order to evaluate the presence of sleep disorders in this subgroup of shift-workers, all the subjects with an ESS scores greater than 11 (a value indicating the first level of pathological sleepiness) underwent a second investigation on sleep disturbances by means of an assisted questionnaire aimed to evaluating the presence of intrinsic sleep disorders.
The questionnaire was subdivided into two groups of questions: the first group included personal-administrative questions on sex, age, civil status, number of children, type of service, role, seniority in shift-work schedules, weight and height. The second group was made up of 13 questions related to sleep and aimed to detect symptoms of narcolepsy (three questions regarding the presence of cataplexy, sleep paralysis and irresistible sleep attacks), obstructive sleep apnea (three questions regarding snoring, nocturnal awakenings with air hunger, nycturia), restless leg syndromes and/or periodic leg movements during sleep (two questions) and difficulties in initiating and maintaining sleep (four questions).
The questions were organized into four ordinal levels "NEVER", "RARELY", "SOMETIMES", "OFTEN" (for instance, *Do you have any difficulty initiating sleep*?, *Do you snore*?, etc.).
Patients were considered positive as to the presence of sleep disturbances only if they responded "sometimes" or "often" to all the items referred to each one of the sleep disturbances explored.
Moreover subjects were asked to respond if they have ever had an accident at work or during driving and if it could be the consequence of excessive sleepiness.

Statistical analysis

The subjects with pathological sleepiness were divided into two groups: with and without clear symptoms of intrinsic sleep disorders. The distributions of age, seniority and number of accidents were evaluated for each group and the between group differences were assessed by means of the chi-squared test (χ^2). Significance was accepted at $p<0,05$.

Results

In 61 subjects (9,9% of the population studied) a pathological level of sleepiness was found.
The mean score of the ESS was 12,4 ranging from 11 to 18 (Fig.1).
Subjects positive for symptoms related to intrinsic sleep disorders were 32 (Table 1). Ten subjects were positive to more than one sleep disorder.
The distribution of age and seniority suggested the prevalence of older subjects in the group with clear symptoms of sleep disturbances but the between group differences did not result statistically significant.
25 subjects positive for symptoms of intrinsic sleep disorders and 14 subjects without sleep disorders referred to have had an accident at work or during driving (χ^2, $p< 0.02$). Moreover 11 subjects positive for sleep disorders and only 3 subjects without sleep disorders referred to have had an accident due to excessive sleepiness.

Discussion

Our investigation revealed a relative high prevalence (9,9 %) of excessive daytime

sleepiness in our sample studied. These data, measured by a standardized method, mirrors the results obtained in other populations of workers (13).

About the 50% of the sample studied had evidence of an intrinsic sleep disorder, even though an accurate diagnosis could not be made by this questionnaire. Subjective reports of sleep habits cannot provide accurate diagnoses to explain excessive daytime sleepiness in terms of sleep disorders. Nevertheless, analysis of the answers to the items of the questionnaires seems to show a high prevalence of sleep disorders that could contribute to shift-workers sleepiness.

A large group of subjects with an ESS scores ≥ 11 did not fall within the criteria of any intrinsic sleep disorders investigated. Their daytime sleepiness could be a consequence of other factors such as an insufficient sleep in the 24 hours. This requires further investigation.

Our results revealed a high prevalence of accidents in subjects positive for sleep disturbances. Moreover a third of the sample with associated sleep disturbances referred to have had an accident at work or driving as a consequence of the excessive sleepiness. Only three subjects in the other group of shift-workers responded in the same way. Sleepiness as a consequence of shift-work per se is known to increase the risk of accidents during the working hours. Our data seems to reveal that such a risk is further increased by the association with intrinsic sleep disorders. The risk of accidents at work is much more relevant when shift-workers, that have to guarantee community safety, are engaged in tasks requiring high performance levels and stressing working conditions as in the case of policemen.

In conclusion our data want to alert occupational health physicians to possible lurking intrinsic sleep disorders worsening health problems in shift-workers.

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Fig.1

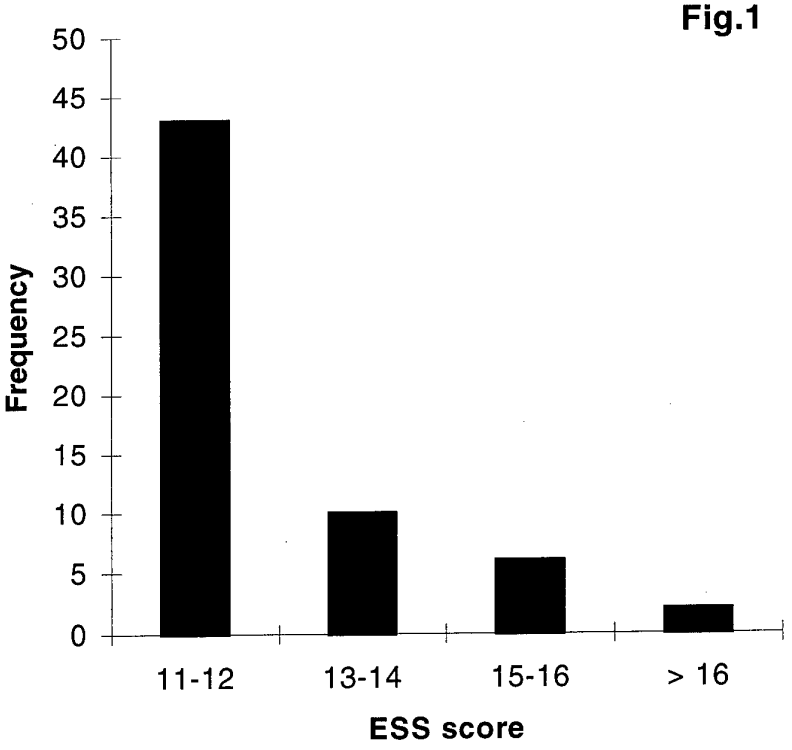

Fig. 1: Frequency distribution of Epworth sleepiness scale.

Table 1: symptoms of sleep disorders derived from the questionnaire

Symptoms of sleep disorders	Number of subjects
None	29
Insomnia	10
Insomnia + RLS / PLMS	3
Insomnia + Narcolepsy	1
OSAS	5
OSAS + Insomnia	3
OSAS + RLS-PLMS	1
OSAS + RLS-PLMS +Insomnia	1
OSAS+RLS-PLMS +Narcolepsy	1
RLS-PLMS	5
Narcolepsy	2

SLEEP INERTIA AND ON-CALL READINESS

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Introduction

The effects of sleep deprivation and chronobiological variations in performance are undoubtedly among the most pervasive limitors of human ability in all situations that require sustained periods of continuous performance and in around-the-clock work settings (e.g. Dinges et al., 1988). These work scenarios are becoming increasingly common, often involving highly skilled and dedicated personnel as in sustained military operations, space flight preparation and launching, crisis and catastrophe management (Mitler et al., 1988). In all these situations, the negative effects of sleep loss during sustained operations must be compared to the adverse effects of sleep inertia upon abrupt awakening from sleep due to a possible emergency (Dinges et al., 1988; Dinges, 1990).

Sleep inertia defines a period of transitory hypovigilance, confusion, disorientation of behavior and impaired cognitive and behavioral performance that immediately follows awakening (Kleitman, 1963). Sleep inertia is one of the most serious contraindications to the use of napping during quasi-continuous operations if the individual may be required to perform complex tasks immediatly after sudden awakening at unpredictable times (Dinges et al., 1985).

Physiological Substratum

Sleep inertia has been considered a "paradoxical" phenomenon (Kleitman, 1963) since performance upon awakening is worse than before sleep. However, physiological phenomena are best described by sinusoidal rather than by square-wave functions (Bertini & Violani, 1992); consequently, the underlying behavioral states cannot readily be switched on and off at the transition to another state. For this reason, if we consider the transition from sleep to wakefulness as a complex process that takes some time to be completed, more than an exact shifting point from one state of consciousness to another, sleep inertia simply becomes the cognitive-behavioral face of this transition process.

From a physiological point of view, during the awakening period a clear dissociation between different parameters is evident. Based on the standard EEG scoring system (Rechtschaffen & Kales, 1968), the awake EEG is identified by a predominant alpha rhythm.

However, the EEG represent only a fraction of all the state-determining factors. In other words, "the presence of all polygraphic features of one state does not mean that no (unmonitored) variables of another state are present" (Mahowald & Schenck, 1992). As an example, Broughton (1968) showed that visual evoked potentials (VEP) recorded upon awakening from slow-wave sleep (SWS) are more similar to those obtained during sleep than to baseline waking values. The author ascribes these results to an impairment of cerebral responsiveness ("functional deafferentation") after SWS awakenings.

Other indications of a slow shift from the sleep EEG substrate to that of wakefulness

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come from the study of the EEG power spectra during spontaneous sleep-wake transitions (Ogilvie & Simons 1992). The FFT analyses of EEG sampled during spontaneous arousals from sleep showed a non-predicted gradual and continued drop of theta and delta power well into the first few minutes of wakefulness. There was a statistically significant difference between sleeping and waking delta only after the subject had behaviorally responded to three consecutive tones (i.e. about 70 sec after the first response).

Similarly, recent studies on cerebral blood flow -CBF- (e.g., Meyer et al., 1987) and cerebral blood flow velocities -CBFV- during sleep (e.g., Hajak et al., 1994; Kuboyama et al., 1997) as indirect but reliable indexes of the underlying neuronal metabolism and activity (e.g., Sokoloff, 1981), also suggest that the periods immediatly following nocturnal and morning awakenings have blood flow characteristics that are not comparable to daytime levels. Moreover, Hajak and co-workers showed that upon morning awakening, subjects required up to half an hour to reach CBFV values corresponding to the waking state of the previous evening. The delayed increases in CBFV after awakening provide another example of dissociation between different physiological parameters of sleep-wake transition, further stressing the slowness of the sleep-wake transition.

Sleep Inertia and Sleep Management

Clearly, sleep inertia has relevant operational implications. As already mentioned in the Introduction, from a sleep-logistic perspective, the main problem is to weigh the effects of sleep loss on sleepiness and performance against the adverse effects of sleep inertia upon abrupt awakening from sleep due to a possible emergency. From this point of view, one of the most critical factors on sleep inertia concerns its duration and time course.

However, although sleep inertia has been incorporated in several models of sleep and vigilance regulation (e.g., Achermann et al., 1994; Akerstedt & Folkard, 1997; Folkard & Akerstedt, 1992), only a few attempts have been made to experimentally quantify its time course. Most authors have typically made only one performance assessment after awakening (e.g. Naitoh et al., 1993), not allowing the determination of the time course and duration of sleep inertia. Due to this methodological limitation, sleep inertia has been generally reported to be short-lasting, being comprised between 1 and 20 minutes (Dinges et al., 1990; Hartmann & Langdon, 1965; Hartmann et al., 1965; Langdon & Hartmann, 1961; Seminara & Shavelson, 1969).

More recently, Achermann and co-workers (1995) addressed this issue by assessing performance every 20 minutes (4 times) during the first hour after awakening from nighttime sleep or from an evening nap, and finally after three hours from each awakening. They found sleep inertia to subside according to an exponential function, and to persist for slightly less than one hour. On the other hand, Jewett and coll. (1999) reported that subjective alertness and cognitive performance reach the baseline waking values about 2 hours after awakening; in this case, too, sleep inertia subsided according to an exponential function. Finally, in an unpublished study from our laboratory (Ferrara et al., unpublished) we found that cognitive performance reaches the baseline level after about 30 minutes from the morning awakening, showing an increasing linear trend during the first 75 minutes after awakening, while sensory-motor and motor performance was still below baseline levels in the same period of time.

Sleep Inertia: Modulating Factors

Sleep inertia duration and magnitude can be modulated by several factors. There are well-known differential effects of REM/NREM sleep stages on performance upon awakening. More specifically, SWS awakenings have greater negative effects on subsequent performance than REM sleep awakenings. These effects have been demonstrated with a wide array of tasks: simple motor tasks (Tebbs & Foulkes, 1966; Wilkinson & Stretton, 1971); sensory-motor tasks (Scott & Snyder, 1968; Feltin & Broughton, 1968); and cognitive tasks (Scott & Snyder, 1968; Stones, 1977).

However, it has been claimed that sleep structure is also very important in determining sleep inertia (Dinges, 1990). The profound modification in sleep architecture and the increased sleep depth caused by sleep deprivation dramatically exacerbate sleep inertia and cognitive impairment upon awakening from recovery sleep (Dinges et al., 1985). It has also been found that cognitive decrements after abrupt awakenings from 1 and 2 hour naps show a linear relationship with SWS amount during the nap (Dinges et al., 1981; 1985).

Moreover, the negative influence of sleep deprivation on sleep inertia seems to interact with time-of-night or circadian factors in producing even more dramatic effects. As an example, Naitoh (1981) reported that, after a 2-hour nap taken early in the morning (0400-0600) following 45 hours of continuous work without sleep, both task performance and self rating of mood, sleepiness and fatigue remain deteriorated at the levels of those who stayed awake.

More generally, the outcomes concerning the modulation of sleep inertia by circadian factors - mainly linked to body temperature rhythm - are not consistent. Conflicting evidence comes from studies of napping with and without previous sleep deprivation (e.g., Bonnet & Arand, 1995; Tassi et al., 1992; Naitoh et al., 1993), as well as from repeated awakenings during nocturnal sleep (e.g., Balkin & Badia, 1988; Rosa et al., 1983; Rosa & Bonnet, 1985). A more accurate description of circadian influences on sleep inertia needs the support of further empirical data.

Moreover, sleep inertia seems to dramatically depend on the type of task used, highly demanding cognitive and attentional tasks being much more affected than simple motor ones (Muzet et al., 1995). At variance with physiological sleepiness, which in self-paced tasks affects speed of performance more than accuracy, it has been claimed that sleep inertia exerts a negative influence on both, but particularly on the latter (Balkin & Badia, 1988; Naitoh et al., 1993; Ferrara et al., unpublished b).

In conclusion, although it is often difficult to compare results of studies on sleep inertia, since several different experimental designs and tasks have been used, a few clear indications seem to emerge. The intensity of sleep inertia is strongly influenced by some homeostatic sleep variables linked to SWS amount and, more generally, to depth of and pressure for sleep. Finally, circadian factors and previous sleep loss exacerbate sleep inertia by adding their simple effects.

Sleep Inertia: Possible Countermeasures

From a brief review of the literature on the physiological basis and modulating factors of sleep inertia, we will try to extrapolate some countermeasures against the detrimental effects of sleep inertia on performance upon awakening, to be applied when it is possible in operational settings.

The first countermeasure could be to reduce the probability of awakening out of SWS, since it is well known that SWS awakenings yield the greatest performance decrements. One possibility is to allow sleep when the occurence of SWS is very low (e.g., in the morning). Another strategy can be to allow naps of about 80-90 minutes (i.e., the mean duration of a normal NREM-REM sleep cycle), minimizing the probability of a SWS awakening. Some experimental data confirm the usefulness of this strategy, by showing that sleep inertia magnitude after a 20-min and a 80-min nap are very similar, while the worst performance upon awakening is recorded after a 50-min nap (Stampi, 1992). Obviously, a 80-min nap should be preferred to a 20-min nap because of its greater restorative power.

Another very important strategy to minimize sleep inertia is to avoid a long period of wakefulness before allowing a nap, since the increase of sleep depth caused by sleep deprivation dramatically exacerbates sleep inertia (Dinges et al., 1985).

In addition, awakening near the circadian nadir of body temperature should also be avoided, especially if the sleep period follows sleep deprivation (Naitoh, 1981).

It has been reported that washing one's face with cold water immediately after awakening is a simple but effective tool to fight sleep inertia (Labuc, 1978, 1979). More generally, every "alerting" factor (i.e., noise, light, physical exercise) should be useful in counteracting sleep inertia, even though - at present - only few attempts have been made to assess their effectiveness. As an example, pink noise (75 dBA) administered during the first hour after awakening improves response speed at 0500 but not at 0800, when it has detrimental effects on performance (Tassi et al., 1993). More recently, it has been reported that following the "normal morning routine" (i.e., getting out of bed, taking a shower, having breakfast) does not abolish sleep inertia as compared to a constant routine in bed (Jewett et al., 1999). In the same experiment (Jewett et al., 1999), it was found that exposure to normal room light (about 150 lux) upon awakening did not improve performance as compared to very dim light (about 20-25 lux).

Sleep Inertia: Open Questions

Sleep inertia is still a poorly understood phenomenon: from the point of view of its physiological substratum, that could be approached in the near future with the newest and more sophisticated neuroimaging techniques; as regards the sleep-related modulating factors and psychological and personality variables that may influence it. However, a few research areas that should be explored to give important answers on sleep inertia to be applied in operational fields will be pointed out.

The first unexplored topic is the role of individual differences in reactions to the effects of sleep inertia. We all anecdotally know that individuals show a wide range of variation with respect to their perceived ability to function immediately after awakening. However, the literature on sleep inertia has definitely ignored this problem, relegating individual differences to a role of "confusing variable" to be controlled. The study of individual differences modulation of sleep inertia will add very important knowledge to the definition of the psychophysiological profile of tolerance to irregular work hours.

The same applies to the role of psychological factors, like motivation, in the modulation of sleep inertia. One should believe that motivation can be a strong and

efficient countermeasure to sleep inertia for a fighter pilot sleeping on-call, when he is requested to be in the cockpit at 5000-10000 metres a.s.l. just 5 minutes after abrupt awakening. However, this topic should be specifically evaluated.

For operational purposes, the duration and time course of sleep inertia after naps taken at different times of the day should also be further assessed, since available data are inconclusive.

It would be very important to have some pharmacological countermeasures to sleep inertia, such as very fast acting stimulants, to be used in operational settings when the need for high levels of alertness and performance immediately after awakening should arise. To our best knowledge, the use of stimulants to counteract sleep inertia effects has never been tried, not even in laboratory settings.

Non-pharmacological countermeasures to sleep inertia could also be very useful, particularly because pharmacological measures are currently lacking. Generally speaking, any alerting factor could be assessed to counteract sleep inertia: physical and/or mental exercise, external noise, bright light. As regards noise, although in at least one study pink noise has been administered for one hour after awakening with non-univocal results (Tassi et al., 1993), the effectiveness of different types of noise with different intensities and durations should be assessed. Bright light might also be effective against sleep inertia, since its alerting effects are well established (e.g., Czeisler et al., 1990).

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INFLUENCE OF AGE AND GENDER ON JET-LAG SYNDROME : RECOMMENDATIONS

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• ABSTRACT

Jet-lag syndrome in civilian flight personnel is quite well known. In Air Force crews, especially during long-haul flights, jet-lag is associated with sleep deprivation and a specific environment. In this communication, we present some results of a real world experiment (simulation of troops deployement) after a transmeridian flight in which we evaluated notably the influence of age and gender in this kind of jet-lag. In our population, composed of 27 US Air Force reservists, males and females from 19 to 46 years old, we did not find any important differences due to age and/or gender. Only subjective data, recorded from Sleep Log, presented statistical differencies. Nevertheless in the global population the jet-lag induced disturbancies in 33% of the studied parameters.
Some physiological and/or pharmacological recommendations are done.

• INTRODUCTION

A lot of civilian and also military people, especially pilots during long-haul flights, suffer from jet-lag syndrome. Symptoms are different during military flights, for example during a troops deployment. Before studying effects of this particular type of jet-lag and evaluating the influence of age and/or gender, we would like to start with a brief summary of the jet-lag syndrome. We will continue with an example of jet-lag syndrome in a military situation, and conclude with few recommendations.

• JET-LAG SYNDROME

The signification of jet-lag is : "Jet engine airliner time lag syndrome". The clinical symptoms observed are due to rapid and repeated transmeridian flights (more than 4 hours) (2).
The symptoms could be divided in acute and chronic effects. The first effects are composed of sleep disturbancies with nocturnal insomnia and diurnal drowsiness, reduction of physical and cognitive performances, digestive disturbancies ; subjects feel a sensation of discomfort, they are sometimes irritable. The flying personnel could present chronic effects of jet-lag too, such as gastric ulcers, intestinal disorders, chronic fatigue with insomnia and sometimes a nervous breakdown.
The jet-lag etiology is not well known. Three aspects are concerned : the fatigue due to travel (seen also in north-south flights), the slowness and irregularity to adjust endogenous rhythm to new local hour (at least the sleep deprivation) and the capacity to react to this troubles by sleep recovery.

• VARIABILITY PARAMETERS OF JET-LAG SYNDROME

Individual parameters	Environmental parameters
- Age	- Flight direction
- Gender	- Noise and temperature levels
- Big and small sleepers	- Conflict intensity
- Morningness and eveningness type	- Bedding
- Sensitivity to sleep deprivation	- Psychosocial environment

Generally we can distinguish individual parameters and environmental parameters.
It is usual to say that age and sometimes gender have an influence on jet-lag effects. There is also a difference between big and small sleepers (*i.e.* subjects who sleep 5 hours per night and whose who sleep 9-10 hours). The morningness and eveningness type, the sensitivity to sleep deprivation seem to be important too (1, 2).
The most famous environmental parameter is the flight direction : generally an eastbound flight is more penalizing than a westbound flight (1). Noise, temperature levels and bedding are important too. At least the intensity of the conflict and the psychosocial environment, especially during a military operation, are some very important parameters.

• "PEGASUS OPERATION" : Experimental protocol

(During the oral presentation, a movie of 15 minutes about the protocol of PEGASUS OPERATION was showed)

To illustrate effects of jet-lag and especially the influence of age and/or gender, we present some results

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from a real world experiment called "PEGASUS OPERATION". It is an exemple of troops deployment which induces jet-lag and limited sleep deprivation. This situation provokes fatigue and a decrease of vigilance and performance.
It was an original collaboration between french Air Force, US Air Force, IMASSA (Institut de Médecine Aérospatiale), Armstrong Laboratory and NESTLE Company.
This unique experiment included 3 military planes (KC 135), 60 people were involved. A jet-lag of 7 hours was due to a transmeridian flight between San Antonio (USA) and Mont de Marsan (France), in an operational setting with a representative population (27 healthy subjects, males and females, reservists from US Air Force).
During this experiment we evaluated the subjective and objective vigilance, the physical and cognitive performances, hormonal proportions, and some physiological parameters, *i.e.* 140 parameters.

Measure of physical static performance with Grip test on an US Air Force reservist (Pegasus Operation)

These parameters were evaluated during two periods of tests, one on mornings (between 0900 and 1200) and another one on afternoons (between 1400 and 1700) and were recorded before the flight (reference period during 2 days) and after the flight (recovery period during 10 days). Each period included : MSLT, VAS, Sleep Log, CFFF, Attention test, STRES battery, Grip test, Jump test and a clinical examination. Other parameters were evaluated at different moments of the day or the night : temperature, actimetry, VAS (during the flight), EEG, salivary samples (cortisol, melatonin, caffeine).
In this protocol, we compared three situations : placebo versus melatonin versus slow release caffeine (a new galenic form of caffeine : STINERGIC®).
In this paper we interest only in placebo group.

• MAIN RESULTS AND DISCUSSION

- Summary of the influence of jet-lag

When we studied the global effect of jet-lag, *i.e.* for males and females of all ages, we observed that 46 parameters on 140, were disturbed or modified *i.e.* 33%.
These data demonstrate the global penalizing effects of jet-lag on a very large population (men, women from 19 to 46 years old) by means of a large choice of tests (biological, physiological, electrophysiological,...). Results demonstrate that the tests used were sensitive to jet-lag.

- Influence of gender

In any case, when a difference existed between males and females, in reference period, it was found again in the post-flight period, *i.e.* that jet-lag did not modified differences previously observed.
When any difference existed in reference period between males and females, one appeared in Sleep Log parameters only during the first five days.
Females were the most sensitive to jet-lag.
If we compare our results to litterature data, the lack of influence of gender on jet-lag is found again (6). The only difference concerns one of the subjective data (Sleep Log) ; but few studies evaluate this parameter.

- Influence of age

Some differences were observed in Visual Analogue Scales, in Sleep Log parameters and also in clinical parameters (orthostatic heart frequency for example).
Subjects less than 35 years old reacted better than olders.
No influence of age was found in other parameters.
More differences are found in the litterature (5, 7, 8) : subjects are generally older than in our case ; in middle age and elderly, physical and cognitive performances are disturbed.

• RECOMMENDATIONS

Between 20 and 45 years old, it is advised to take some counter-measures to beat jet-lag but NO SPECIFIC counter-measures are strictly necessary, if you are a female between 35 and 45 years old.
After the middle age, females should take physiologic or pharmacologic measures to counteract jet-lag.
In the case of an operational situation, recommendations are :
- to stay awake after a transmeridian flight is recommended to expose himself to day light, to participate to social activities and to do physical exercise. It is possible also to major the efficiency of these measures or to replace them, by taking a pill of slow release caffeine (STINERGIC®) (3).
- to facilitate sleep recovery, it is not recommended to sleep during the 10 hours preceding time to go to bed (in local time), but taking a pill of zolpidem (STILNOX®, AMBIEN®,...) just before going to a good bed as confortable as possible is recommended (3).
But in an operational setting, we do not recommand taking melatonin as an hypnotic or a chronobiotic substance, if the right dose and the right time of administration are not well known in your case. Too much coffee (caffeine solution), because of its side effects, is not recommended ; alcohol is prohibited (4).

• CONCLUSION

In military condition the influence of age and gender in jet-lag syndrome seems to be limited. Some easy and safe countermeasures exist to facilitate recovery after an operationnal transmeridian flight.

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The Adaptability of Individuals to Shiftwork. A Possible Experimental Approach.

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Introduction

The Institute for Occupational Physiology at the University of Dortmund has been an important research center for shiftwork. This line of research was terminated a decade ago, when Joseph Rutenfranz died in 1989 and Peter Knauth became Professor at the University of Karlsruhe. Now, this topic will be resumed by a scientist with an extended experience in sleep research focused on experimental studies and field observations on sleep disturbances as caused by environmental noise [10, 11]. Research on shiftwork now will be executed in close cooperation with the biochemical unit of the institute.

The project outlined here is still in the stage of planning, the first part will probably start within some weeks. It aims at the clarification of the individually determined ability to adapt to shiftwork and the question whether and by which tests this ability can be diagnosed during medical occupational check-ups. This is particularly relevant for those organisations, e.g. the army where the personnel operate with extremely expensive worktools and/or whose professional activities may impose a considerable hazard to others.

Shiftwork

At present, 15 – 20 % of the employees in the European Union are performing shiftwork. In many industrial sectors as well as in the army missions during the night are not only planned at long-term but also ordered at short-term. The immediate consequences of these shifts, from day- to nightshifts and the reverse, from night- to dayshifts are desynchronizations of physiological functions. These disturbances are – among others – characterized by impairments of sleep, of well-being, and performance. Additionally, spontaneous sleep periods are expected to occur in about one fifth of the employees during work [1] and thought to play a major role in many accidents [15, 22]. The full adaptation to the new time regimen needs one day on the average per hour of relative time shift. Repeated time shifts, i.e. repeated adaptations to nightshifts and readaptations to dayshifts evoke repeated stress for the whole organism and may accelerate the genesis and manifestation of nonspecific chronic diseases for persons with increased vulnerability in the long run [23].

Circadian rhythm

The circadian rhythm is controlled by the light-dark cycle and mediated by melatonin, the hormone that is produced in the pineal gland. It adopts the role of a pacemaker for the synchronization of physiological

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functions (core temperature, heart rate etc. [3, 4]).

The temporal course of the melatonin synthesis is closely related to the periodical alterations of body core temperature which was and is still usually registered in studies on the circadian rhythm and the effects of shiftwork. As the production of melatonin is directly controlled by the endogenous pacemaker the actual concentration of that hormone is a more reliable indicator of the individual circadian phase and of related disorders than rectal temperature, in particular, as the latter is more sensitive to masking effects due to different environmental influences. The major advantage of the registration of rectal temperatures is that this variable can be recorded continuously and at low costs.

Inhibition of the melatonin synthesis

The production of melatonin is not only inhibited by natural but also by artificial light; hereby wavelength, intensity and duration of light play an important role [5, 6, 13, 21, 25]. The direction of the light-induced phase shift depends also on the time of application. Light in the evening causes phase delays whereas light in the morning leads to phase advances [14]. It is therefore concluded that adaptation to nightwork can be facilitated by the application of light.

The success of those measures is, however, debated as shiftworkers are exposed to contradictory zeitgebers [12, 17]. Additionally, due to the interindividual extremely different phases (up to 10 hours, morning-, evening types), the effects of light that is applied at a defined time of the day must evoke different effects in different persons [7, 8, 18, 19, 20]. Moreover, in the real situation various other competing zeitgebers might influence the organism, e.g. other parts of the electromagnetic spectrum (UV-A radiation, low-frequency magnetic fields).

Adaptation to shiftwork

Several studies revealed that a certain percentage of individuals is not able to adapt to shiftwork. Some authors reported that particularly those persons with a late circadian phase (evening types) have only minor difficulties to cope with nightwork [16]; where other authors reported the same for persons with a smaller amplitude of their core temperature ('individuals with low amplitudes have less to invert and adapt more easily' [2, 24]). A clear allocation between person-related characteristics and the ability to adapt to shiftwork, is at present, however, not possible. Based on a few studies on this problem and on the strong correlation of body core temperature on the one hand and the amount and the course of melatonin synthesis on the other hand it is possible to derive the hypothesis that persons with late circadian phases (evening types) and small amplitudes of their body core temperature produce less melatonin and adapt better to shiftwork than persons with early circadian phases (morning types).

Hypothesis: A late circadian phase is associated with a low amplitude of rectal temperature and of melatonin production. Those persons adapt more easily to shiftwork than those with an early circadian phase, with high amplitudes of rectal temperature and of melatonin production.

An important aspect of the intended studies is therefore the question of an individual characteristic of melatonin production and a concomitant individual adaptability to shiftwork.

Outline of the project

The project will be executed in four steps, where the hypotheses, the procedure and the methods applied may deviate to those presented below according to the results of the preceding step(s):

[1] **Step 1 (pilot study)** aims at the determination of the relationship between subjective circadian phase and the amount of melatonin production during the night.

[2] **Step 2 (constant routines)** will be performed to examine the relationship between subjective circadian phase and the course and the amplitudes of rectal temperature and of melatonin production over a time period of 24 hours.

[3] **Step 3 (experimental shiftwork)** is planned to elucidate the role of individual characteristics for the adaptability to nightwork under strictly controlled conditions in the lab, i.e. to determine the resistance to adapt to nightwork even in case of facilitating measures.

[4] **Step 4 (prospective study)** aims to clarify whether an individual adaptability to nightshifts can be predicted on the basis of individual features.

Methods

Step 1 – Hypothesis: A late subjective circadian phase is associated with a late melatonin peak and a low melatonin production.

The **pilot study** shall elucidate the assumed relationship between the individual circadian phase, the course and the amount of melatonin production. The hypothesis is that the quantity of melatonin production is lower and the peak of melatonin production is later in persons with a self-rated late circadian phase (evening types) as compared to persons with an early phase (morning types).
About 100 patients of the surgical unit of a military hospital fill in a questionnaire which proved to be a valid instrument for the determination of the subjective circadian phase. The actual concentration of salivary melatonin of these persons will be determined hourly during one night (6 pm to 6 am) and the excretion of 6-hydroxymelatonin sulfate at 3 hour intervals. This time space is sufficient to determine reliably the maximum of melatonin synthesis during the night. Personality variables will be determined by suitable inventories (Freiburg Personality Inventory, FPI). A military hospital is chosen for that pilot study as the respective patients are relatively young and healthy. Those with internal diseases are excluded from participation.

Step 2 – Hypothesis: The course and the amplitude of body core temperature is closely related to the course and the peak of melatonin production (and with the self-rated circadian phase).

The **constant routines** consist of 24-hour-observations to determine the relation between the subjectively rated circadian phase, the course and the amplitude of rectal temperature and of melatonin production: Due to economical reasons these observations shall be designed as the basis for the prospective study outlined under step 4 and therefore performed with persons who regularly or occasionally work at night during their professional carrier. 100 to 200 persons fill in a questionnaire

(the same as in the pilot study) to determine the subjective circadian phase and spend 24 hours (noon to noon) under constant conditions (< 50 lux). This procedure (constant routines) is according to an agreed opinion of several authors essential to determine the actual circadian phase with sufficient accuracy [25].
During the observation period the actual concentration of salivary melatonin will be measured hourly, the excretion of 6-hydroxymelatonin sulfate for every 3 hour-periods. Rectal temperatures, heart rates, and body movements shall be recorded continuously throughout. Personality variables will be determined with a suitable inventory (FPI).
The results of the pilot study and the constant routines determine the extent of the third and the fourth step.

Step 3 – Hypothesis: Individual features (self-rated circadian phase / course and amplitude of body core temperature or of melatonin production) determine the inability to adapt to shiftwork. This resistance is expected even in case of targeted facilitations.

Experimental shiftwork under strictly controlled conditions shall be performed as the effects expected here might be considerably masked due to a vast number of environmental influences that are unavoidable in the real situation at the workplace.
Exposure to light suppresses the synthesis of melatonin and has been shown to facilitate the process of adaptation to nightwork. If the suppression of melatonin synthesis is – as reported by Graham et al. [9] – greater in persons with habitually low melatonin levels, these persons are expected to be even more resistant against adaptation in case of targeted exposure to bright light.
After the individual circadian phase is determined using a constant routine persons with early and with late circadian phases (habitually high and low levels of melatonin production, high and low amplitudes of core temperatures) will be observed during 2 systematically permuted experimental shiftwork periods which are separated by 4 weeks. These studies are at present roughly planned. An adjustment of the design, the procedure, and the methods might be necessary due to the results of Steps 1 and 2, as well as to the then available knowledge provided by the studies of other authors. In principle, two or three days of dayshift will be followed by 5 days of nightwork. During one experiment, adaptation to night work will be facilitated by bright light that is individually applied according to the results of the constant routine in such a way that it causes a phase delay.
Physiological, psychological, and biochemical parameters that are likely to be influenced by the alterations of the circadian rhythm will be recorded as well as the respective effects on the ultradian rhythmicity, particularly on sleep. During the entire observation period core temperatures, heart rates and body movements will be recorded continuously throughout, the excretion of 6-hydroxymelatonin sulfate for every 3-hours period, and the electrophysiological indicators of sleep depth during the night. As melatonin is much less sensitive to masking than rectal temperature, the actual concentration of plasma melatonin will be determined hourly during the 24 hours of the last dayshift and the 24 hour period of the 3rd nightshift. During the time awake several tests concerning mental performance, such as implicite learning which proved to be sensitive against sleep disorders will be performed.

Step 4 – Hypothesis: Individual features (self-rated circadian phase / course and amplitude of body core temperature or of melatonin production) are reliable predictors for the ability to adapt to shiftwork.

The **prospective study** aims at the clarification, whether and to what extent the amount and the course of individual melatonin production correlates with the adaptability to shiftwork. Those persons who were investigated in the 2nd part of the study shall be asked to participate again after they had finished their education and worked in their profession for at least one year. First these persons complete again the questionnaire on subjective circadian phase and another questionnaire where they state their experience with shiftwork. As it cannot be expected that persons who had only recently finished their professional education and started their job frankly admit if they have serious problems with shiftwork, objective physiological measures are advisable. Body core temperatures and heart rates will be measured continuously and the excretion of 6-hydroxymelatonin sulfate for every 3-hours period. Actual concentration of plasma melatonin will be determined hourly during the 24 hour period of the last dayshift and the 24 hour period of the 3rd nightshift. These respective 2 nights shall be spent in the laboratory.

As the ability to adapt to shiftwork is supposed to be related to the individual circadian phase and persons with extreme phases (morning-, evening types) respectively persons with extremely low or high melatonin production are relatively seldom in the total population, it is necessary to arrange night shifts particularly for those persons (dependent on the results of part 2).

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NAPPING STRATEGIES TO COUNTERACT SLEEP DEPRIVATION

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Introduction

There is an abundance of evidence indicating that a nap taken during long periods of otherwise continuous wakefulness is extremely beneficial for improving alertness and performance.[4,5,9,13,15,17,25,26,31] However, scheduling naps is not a simple matter. Several factors are important to consider before implementing a napping regime into a continuous operations scenario.

Nap timing

One important factor in scheduling naps is placing them at optimal times with regard to the amount of sleep loss. A nap taken during the day before an all-night work shift (a prophylactic nap), with no sleep loss prior to the shift, will result in improved performance over the night compared to performance without the nap. Although naps taken later in the sleep-deprivation period also are beneficial, these naps probably should be longer than prophylactic naps in order to derive the same performance benefit. Schweitzer, Muehlback, and Walsh[28] measured performance and alertness in subjects who received a 2- to 3-hour nap before a night work shift (with concurrent sleep loss). Although the usual circadian trough was seen in the early morning, the nap attenuated the decline in performance compared to a night where no nap was taken prior to the shift.

In a study conducted by Bonnet[5], a nap before a 52-hour continuous performance period was beneficial in keeping performance and alertness from decreasing for up to 24 hours compared to the no-nap condition. However, by the second night of sleep loss, the benefit of the naps could not be reliably measured. In a study by Naitoh and colleagues[18], subjects were given a 3-hour nap after being awake for approximately 24 hours, but then were required to stay awake an additional 20 hours. Results indicated that this 3-hour nap reduced the decline in performance during the additional work period. While naps taken prior to extended periods of sleep loss, "prophylactic naps," do not totally eliminate the circadian dip seen in the early morning (around 0500), the degradation in both cognitive performance and alertness is attenuated compared to no napping conditions.[4,6,10,11,19]

Nap length

Another factor to consider when scheduling naps during continuous operations is nap length. Most studies indicate that naps from 1 hour to 8 hours will improve performance and alertness during continuous operations. A relationship between nap length and performance was reported by Bonnet[5] based on a study in which subjects were allowed either a 2, 4, or 8-hour nap before 52 hours of continuous operations. The results indicated a dose-response relationship between the length of the nap and performance during the first 24 hours of sleep deprivation. Bonnet concluded that the nap before an all-night shift should be as long as possible to produce maximum performance benefits, and that prophylactic naps were better than naps designed to replace sleep that was already lost due to requirements for continuous wakefulness.

An investigation by Lumley and colleagues[14] in which subjects were deprived of sleep for 24 hours and then permitted naps of either 15, 30, 60, or 120 minutes, indicated that alertness increased as a function of increased nap length, with the highest level of alertness occurring after the 60-minute nap. There was, however, no difference between the 60-minute nap and the 120-minute nap, possibly due to sleep fragmentation in the longer period.

Nap placement and the circadian phase

Another factor to consider when planning a napping strategy for use during continuous operations is where the nap should be placed in the circadian phase. Nap timing should take into account the ease of falling asleep at various times, the quality of sleep as a function of the body's internal clock, and the effects on performance both immediately after awakening and later in the work period. Sleep tendency is highest when core body temperature is in its trough (in the early morning hours) and lowest when core body temperature is in its peak (in the early evening hours).[7] Thus, there may be significant problems initiating and/or maintaining a nap during times when core temperature is high, termed the "forbidden zone" for sleep.[12]

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Naps which are placed during the circadian troughs are the easiest to maintain and they show beneficial effects on later performance. When naps placed in the circadian trough are compared to naps placed in the circadian peak, the effects on performance are different. Gillberg[10] examined the effects of a 1-hour nap placed either at 2100 or 0430 after 24 hours of sleep deprivation. Both naps improved performance the following morning when compared to a no-nap group, but the nap taken at 0430 (in the circadian trough) showed the most benefit. While a nap taken anywhere in the circadian cycle before sleep deprivation is beneficial in maintaining performance across the sleep loss period, there is a high cost to napping during the early morning (during the circadian trough). Although naps during the circadian trough may be more effective for performance sustainment (and they are easier to initiate and maintain), they also are the more difficult naps from which to awaken. Generally, studies have shown that post-nap sleepiness, termed "sleep inertia," is higher and performance is lower immediately upon awakening from a nap taken during the circadian trough as compared to naps taken during the circadian peak.[8]

Regardless of the time of the nap, sleep inertia will occur, and work requirements should be delayed accordingly. Performance generally will be lowest during the first 5 minutes after awakening, but it usually recovers after 15 to 30 minutes.[8] Generally, sleep inertia will be extended in situations where the timing of the nap is misplaced and/or the amount of sleep deprivation is extensive before the nap occurs. Thus, Dinges et al[8] suggest that during continuous operations, naps in the circadian trough should be avoided, and naps should be taken before a person's sleep loss extends beyond 36 hours. However, it should be possible to take advantage of the improved quality of naps in the circadian trough while avoiding the sleep-inertia effects if napping personnel can be awakened about 1 hour prior to their work shifts.

Summary

In summary, naps are beneficial for reducing sleepiness and performance decrements during sleep-deprivation periods. However, before scheduling naps during continuous operations, several factors should be taken into account. A nap is most beneficial if taken before significant sleep loss occurs if it is as long as possible and if it is placed in the circadian trough (provided there is time to recover from sleep inertia).

Unfortunately, work demands and staff shortages make scheduling naps in the real world problematic. It may not be possible to schedule naps during times when personnel will find it easy to sleep (during circadian troughs). In addition, the anxiety, noise, heat, and environmental lighting present in operational scenarios may impair the ability of personnel to initiate and maintain effective sleep. Thus, in order to provide a way for personnel to obtain needed sleep whenever the opportunity to sleep occurs, a short-acting sleeping aid such as zolpidem tartrate may be useful.

Zolpidem tartrate, a non-benzodiazepine hypnotic of the imidazopyridine class, is supplied in 5 and 10 mg tablets for oral administration.[21] It has a mean elimination half-life of 1.7 hours (se=0.1)[30] and few daytime residual effects.[3] The recommended dose is 10 mg given immediately before bedtime. Most studies indicate that next-day performance is not affected by nighttime administration of 5 or 10 mg of zolpidem tartrate.[22,24,27,29] Higher dosages (20 mg) have been found to mildly affect next-day performance[1], but even at this dosage, there have been few residual effects.[2]

Study Questions

Since research indicates that taking a nap prior to sleep loss can help offset performance decrements seen during extended work schedules, napping should be beneficial in sustained operations. However, if people are unable to place naps at optimal times or if they are unable to sleep because of situational factors (i.e., heat, noise, light), zolpidem tartrate may be useful.

The first question addressed by this experiment was whether a 2-hour nap, placed late in the evening (during the "forbidden sleep zone"), would affect the performance, mood, and sleepiness of aviators during a continuous operations scenario. The second question was whether zolpidem tartrate could be effectively used to promote naps (and thus enhance the performance-sustaining effects of naps) during times when sleep was not expected to come readily.

Methods

Subjects

Eighteen male aviators between the ages of 22 and 31 (mean of 24.4) and weighing between 145 and 205 pounds (mean of 177.6) participated after medical pre-screening.

Procedure

During three sleep deprivation periods, subjects completed cognitive tests, electrophysiological evaluations, and questionnaires. Subjects were tested following a 2-hour nap induced with zolpidem (Znap), a 2-hour nap without zolpidem (Pnap), and a 2-hour forced-rest period (Nonap). The study was fully counter-balanced and double-blind.

Testing schedule. Subjects were tested in pairs and were housed in the U.S. Army Aermomedical Laboratory (USAARL) throughout the 9-day testing period. Subjects reported to USAARL on Sunday for electrode attachment,

initial training on the cognitive task, and an adaptation sleep night. On Monday, training began at 0900 after 10 hours of sleep and lasted until 2010 (bedtime was at 2200). On Tuesday, Thursday, and Saturday (the control/intervention days), testing was conducted at the same times as on Monday following 10-hours of sleep; however, rather than receiving a full night's sleep on each of these nights, subjects received one of the interventions--either Pnap, Znap, or Nonap, beginning at 2100 and ending at 2300. All subjects received all three interventions, with subjects being randomly assigned to one of the six possible orders of interventions with the constraint that the orders be fully counterbalanced. On Wednesday, Friday, and Sunday (the test days following interventions), subjects began testing at 0100 and continued until 2010. On the last Monday (following the last sleep-deprivation period), testing was conducted throughout the day. On Tuesday, subjects were released after 10 hours of recovery sleep. Control days (Tuesday, Thursday, and Saturday) were placed between each test day to allow complete drug clearance and recovery from sleep deprivation prior to the next intervention. Subjects were supervised at all times. The schedule is shown in figure 1.

Visual Analog Scales (VAS). The VAS was administered hourly from 0900 to 2000 on control days (and again at 2300 after the nap or forced rest) and from 0100 to 2000 on test days. Subjects rated themselves by marking 100 mm lines centered over the adjectives: "alert/able to concentrate," "anxious," "energetic," "feel confident," "irritable," "jittery/nervous," "sleepy," and "talkative."[20] At the ends of each line, "not at all" and "extremely" were printed respectively. Scores for each adjective consisted of the distance (in millimeters) from the left edge of the line to the mark.

Repeated test of sustained wakefulness (RTSW). The RTSW was performed every 2 hours from 1010 to 2010 on control days and 0210 to 2010 on test days. The subject, who attempted to remain awake while reclined on a bed with eyes closed in a cool, darkened bedroom, was allowed to remain in bed for as long as 20 minutes, but was immediately awakened if he fell asleep. Electroencephalographic (EEG) data were recorded from C3, C4, O1, and O2 referenced to contralateral mastoids (A1 or A2) and scored to determine the time from lights out until the first occurrence of a K complex or sleep spindle. A Nihon Koden electroencephalograph (EEG-4321P) was used with time constants and high filter settings of 0.3 sec. and 35 Hz, respectively.

Sleep architecture of naps. Polysomnograms during naps also were collected with a Nihon Kohden. EEG, electrooculogram (EOG) and electromyogram (EMG) data were recorded throughout napping periods to assess sleep quality. EEG data were recorded from C3, C4, O1, and O2 referenced to contralateral mastoids; EOG data were recorded from electrodes placed at the outer canthus of the left and right eyes; and EMG data were recorded from electrodes attached submentally. Time constants and high filter settings were the same as the RTSW for the EEG; they were set at 5.0 sec. and 10.0 Hz for the EOG, and 0.003 sec. and 120 Hz for the EMG. Nap records were scored according to standard procedures[23] in terms of sleep latency (lights out until the first full minute of stage 2), percentage of time spent in each stage, movement time, and time awake after sleep onset.

Profile of Mood States (POMS). The POMS was administered every 2 hours from 0900 to 1900 on control days and from 0100 to 1900 on test days. The POMS is a 65-adjective scale yielding 6 scores: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment.[16] Subjects were asked to indicate how well each of the mood adjectives described their present feelings. Scores for each of the 6 factors were calculated using template-guided scoring.

Multi-attribute task battery (MATB). The MATB was completed every 4 hours from 0910 to 1710 on control days and 0110 to 1710 on test days. The MATB, a 30-minute, computerized, aviation simulation test, required monitoring simulated aircraft fuel levels (resource management) and warning lights/dials (systems monitoring), while concurrently completing an unstable tracking task and a communications task (following auditory instructions to change "radio frequencies"). Subjects were scored in terms of how quickly and accurately they responded. Specifically, the resource management task yielded mean deviation of units of "fuel" in tanks A and B from the target of 2500; systems monitoring yielded mean reaction time (RT), standard deviation of RT (SDRT), and time-out errors for lights and dials; communications yielded number of time-out errors and mean RT and SDRT for correct responses; and tracking yielded root mean square (RMS) deviations.

Medication administration. Each zolpidem tartrate tablet (10 mg), placed in a white capsule which matched lactose-filled placebos, was administered at 2230 (30 minutes prior to nap time) with approximately 8 ounces of cold water.

Results

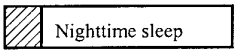
Analysis of variance (ANOVA) with repeated measures on two factors (condition and time) was used to analyze the data (except for the sleep data in which there was only a condition factor). To maintain brevity, only effects which involve the condition factor will be discussed.

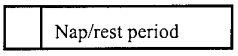
Sleep architecture of naps

Nap data were analyzed with a one-way ANOVA for condition (Znap and Pnap). The variables were minutes in bed; minutes until sleep onset; minutes of sleep; percentage

Time	Sunday	Monday Training	Tuesday Baseline	Wednesday Test	Thursday Recovery	Friday Test	Saturday Recovery	Sunday Test	Monday Recovery	Tuesday
0100				VAS/POMS		VAS/POMS		VAS/POMS		
0110				MATB		MATB		MATB		
0200				VAS/RTSW		VAS/RTSW		VAS/RTSW		
0235				EEG/EP		EEG/EP		EEG/EP		
0300				VAS/POMS		VAS/POMS		VAS/POMS		
0330				MiniSim		MiniSim		MiniSim		
0400				VAS/RTSW		VAS/RTSW		VAS/RTSW		
0500				VAS/POMS		VAS/POMS		VAS/POMS		
0510				MATB		MATB		MATB		
0600				VAS/RTSW		VAS/RTSW		VAS/RTSW		
0635				EEG/EP		EEG/EP		EEG/EP		
0700				VAS/POMS		VAS/POMS		VAS/POMS		
0730				MiniSim		MiniSim		MiniSim		
0800		Wakeup	Wakeup	VAS/RTSW	Wakeup	VAS/RTSW	Wakeup	VAS/RTSW	Wakeup	Wakeup
0830		Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast
0900 0910		VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	Debrief
1000		VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	Release
1035		EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	
1100		VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	
1130		MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	
1200		VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	
1235		Lunch	Lunch	Lunch	Lunch	Lunch	Lunch	Lunch	Lunch	
1300		VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	
1310		MATB	MATB	MATB	MATB	MATB	MATB	MATB	MATB	
1400		VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	
1435		EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	
1500	Arrive	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	
1530	Inservice	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	
1600	Medical	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	
1700 1710	Electrode Hook-up	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	
1800	Hook-up	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	
1835		EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	
1900	Dinner	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	
1930	Training	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	
2000		VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	
2035		Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	
2100		PT	Drug/nap	PT	Drug/nap	PT	Drug/Nap	PT	PT	
2130	Vitals	PT/Shower	OR Rest	PT/Shower	OR Rest	PT/Shower	OR Rest	PT/Shower	PT/Shower	
2205	Lights out	Lights out		Lights out		Lights out		Lights out	Lights out	
2300			Wakeup/VAS		Wakeup/VAS		Wakeup/VAS			
2400			Shower		Shower		Shower			

Figure 1. Testing schedule.
VAS - Visual Analogue Scale; POMS - Profile of Mood States; MATB - Multi-attribute Task Battary; RTSW - Repeated Test of Sustained Wakefulness; EEG - Resting electroencephalogram; EP - evoked potentials; PT - Physical training (exercise)





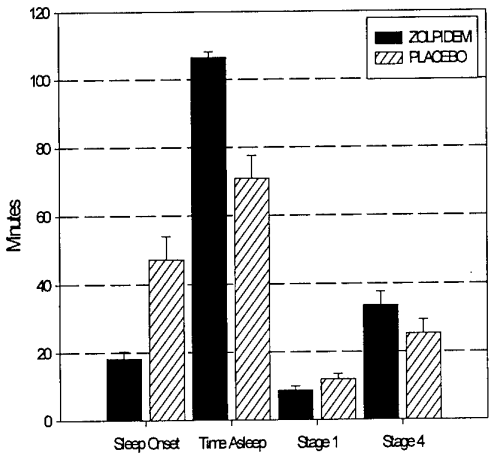


Figure 2. Effects of nap condition on sleep parameters.

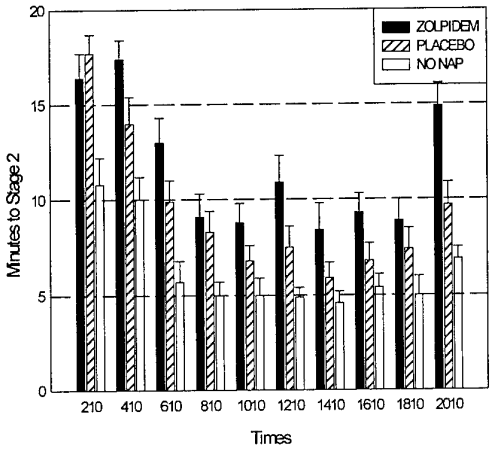


Figure 3. Latency to sleep onset on the RTSW for each napping condition.

of stages 1, 2, 3, 4, and rapid eye movement (REM); percentage of time awake after sleep onset; and movement time. Because one subject was unable to sleep during his zolpidem nap (on the second night of the study) despite being able to sleep during his placebo nap (on the fourth night), his data were excluded from the analysis. The results indicated that there was faster sleep onset, greater minutes of sleep, less stage 1 sleep, and more stage 4 sleep after zolpidem than placebo (see figure 2).

RTSW

The RTSWs, analyzed in a 2-way ANOVA for condition (Znap, Pnap, and Nonap) and time (0210, 0410, 0610, 0810, 1010, 1210, 1410, 1610, 1810, and 2010), indicated a condition-by-time interaction and a condition main effect. The interaction was because differences among the conditions were larger during the first half than the second half of the day (see figure 3). Subjects were better able to remain awake after Znap than after Nonap throughout the testing day; Pnap was better than Nonap except at 1410 and 1610; and Znap was better than Pnap at 0410, 0610, 1210, 1610, and 2010. The condition main effect showed Znap led to improved wakefulness compared to the other interventions, and Pnap was better than Nonap (means were 11.7, 9.4, and 6.3, respectively).

MATB

MATB data were analyzed in a 2-way ANOVA for condition (Znap, Pnap, and Nonap) and time (0110, 0510, 0910, 1310, and 1710). The four tasks were analyzed separately.

Resource management. An examination of the mean deviation of units of "fuel" in tanks A and B from the target of 2500 revealed no significant main effects or interactions.

Communications. The ANOVA on RT and SDRT for correct responses and number of time-out errors indicated a condition-by-time interaction only on RT because of shorter RTs after both Znap and Nonap than Pnap at 1710 (see figure 4).

Systems monitoring. The ANOVA on RT, SDRT, and time-out errors to lights and dials indicated condition-by-time interactions on the RT for lights and dials and SDRT for lights. In each case, there were differences among the conditions only at 0910; the RTs for both lights and dials were faster after Znap than Nonap, the RT for dials was shorter after Pnap than Nonap, and the RT for lights was shorter after Znap than Pnap. SDRT for lights was smaller after Znap than either Pnap or Nonap (see figure 4). A condition main effect on RT for lights revealed a reduction in RT after Znap compared to Nonap.

Tracking. A condition-by-time interaction and a time main effect occurred on RMS errors. The interaction was due to differences among conditions only at 0910 where errors were smaller after Znap than Pnap or Nonap (see figure 4).

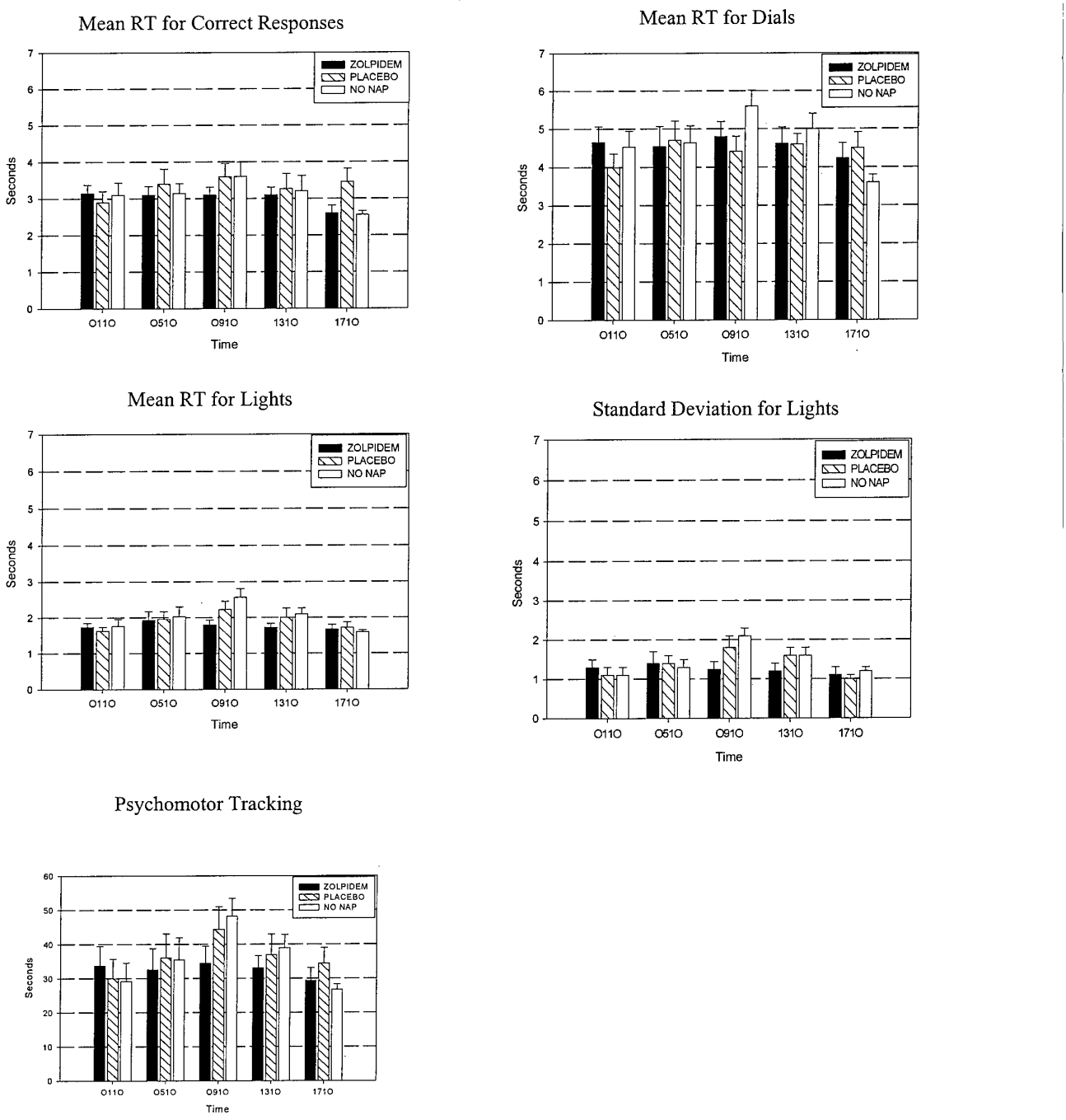


Figure 4. The effects of napping condition on performance of the MATB subtests.

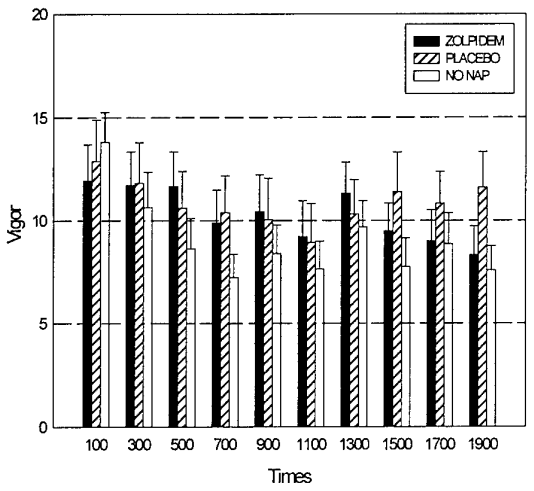


Figure 5. The effects of napping versus forced rest on POMS vigor ratings.

POMS

The ANOVA for condition (Znap, Pnap, and Nonap) and time (0100, 0300, 0500, 0700, 0900, 1100, 1300, 1500, 1700, and 1900) revealed an interaction only on vigor. Znap increased scores relative to Nonap at 0500 and 0700, while Pnap was better than Nonap only at 0700. At 1900, Pnap was better than both Znap and Nonap (see figure 5).

A condition main effect was found on the fatigue scale due to lower fatigue ratings under Znap than Nonap.

VAS

The VAS scores were analyzed in an ANOVA for condition (Znap, Pnap, and Nonap) and time (2300 and hourly from 0100 to 2000). There were condition-by-time interactions on alertness, energy, confidence, irritability, sleepiness, and talkativeness (see figure 6). Most resulted from inertia-related decrements immediately following the naps which later gave way to nap-related improvements. VAS ratings were worse at 2300 after both Znap and Pnap compared to Nonap (alertness was also worse at 0100). However, beyond this time, naps attenuated the declines (except for confidence ratings which were unaffected late in the day). *Alertness* was higher after Znap than Nonap at 0400 and 0500, from 0700 to 1100, and at 2000; higher after Pnap than Nonap at 0400 and from 0700 to 1100; and higher after Znap than Pnap at 0500. *Energy* was higher after Znap than Nonap at 0400, 0500, 0700, and 0800; higher after Pnap than Nonap at 0400, 0700, and 0800; and higher after Znap than Pnap at 0500. *Irritability* was lower after Znap than Nonap from 0400 to 0800, but lower after Pnap only at 0700. Znap was significantly better than Pnap at 0500, 0600, and 0800. *Sleepiness* was reduced by Znap relative to Nonap from 0400 to 0800, at 1500, and from 1700 to 2000; sleepiness was reduced by Pnap relative to Nonap from 0400 to 0800, 1500, 1700, 1900, and 2000; and sleepiness was less after Znap than Pnap only at 2000. *Talkativeness* ratings were higher after both naps at 0500; and higher after Znap compared to Nonap at 0700 as well.

Condition main effects occurred on alertness, irritability, sleepiness, and talkativeness. On every scale, Znap was better than Nonap; Pnap was better than Nonap on sleepiness; and Znap was better than Pnap on irritability.

Discussion

This evaluation of two types of 2-hour prophylactic naps (one induced with 10-mg zolpidem tartrate and the other a "natural", or placebo, nap) during the final 23 hours of a 38-hour period of continuous wakefulness supported previous findings which indicated both naps were superior to a forced-rest condition in terms of sustaining alertness. Comparisons between the zolpidem and placebo naps indicated the zolpidem nap was superior in several instances.

Sleep architecture of naps

The more rapid sleep onset and longer sleep duration in the zolpidem nap compared to the natural nap are consistent with other reports.[13,27] Since subjects were provided with only 2 hours for each nap, zolpidem provided significantly more sleep than placebo. Subjects fell asleep almost twice as fast after zolpidem tartrate (24 minutes) than after placebo (46 minutes), and this no doubt contributed to the mild superiority of the zolpidem nap.

Sleepiness evaluations

Decrements in VAS alertness and energy ratings, coupled with increased irritability and sleepiness, were more pronounced after forced-rest than after one or both napping conditions, and the zolpidem nap often was superior to placebo. Of the 30 significant effects among conditions at various times, 97 percent were because the zolpidem-induced nap was better than forced rest; 63 percent were because the placebo nap was better than forced rest; and 20 percent were a result of better VAS ratings after the zolpidem nap than after the placebo nap.

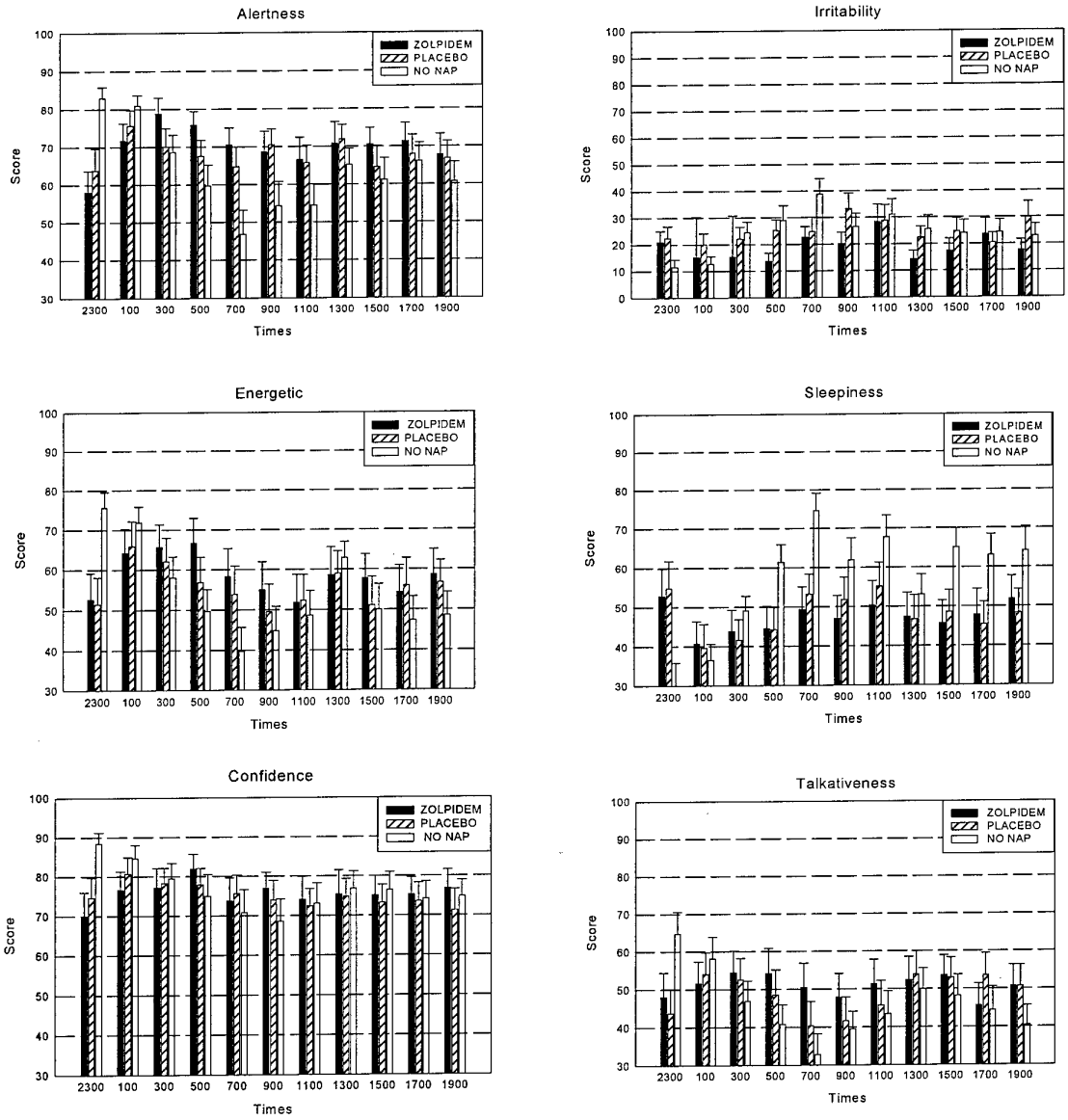


Figure 6. The effects of napping condition on VAS mood scales.

VAS ratings in the present study were consistent with RTSWs which indicated subjects could remain awake longer after the zolpidem nap than after the placebo nap or after rest only. It appears that the zolpidem naps were superior to placebo naps; alertness was greater after the zolpidem nap in comparison to forced rest during 100 percent of the RTSWs; greater after the placebo nap than after forced rest in 80 percent; and greater after the zolpidem nap than after the placebo nap in 50 percent of the RTSWs.

Unfortunately, the benefits from napping were not apparent immediately after subjects were awakened. VAS data collected at about 5 minutes after awakening from the 2-hour naps revealed that feelings of alertness, energy, confidence, and talkativeness were lower after both the zolpidem and placebo naps than after the forced-rest condition. In addition, ratings of irritability and sleepiness were higher after both naps than after forced rest. The mood effects disappeared by the time of the next VAS (about 2 hours after awakening from the naps), with the exception of the alertness decrement which persisted until, but not beyond, 0100. If measurements of mood had been obtained more frequently, there may have been increases in mood before 2 hours had lapsed. It is also unclear whether performance suffered along with mood during these times because the first test was not given until 2 hours after the nap; however, it has been suggested that mood disruptions caused by sleep inertia outlast performance decrements.[9] Postnap inertia was not more severe after zolpidem than placebo. Initially, there did appear to be a slight hangover effect on the ratings from several scales; however, none of these were statistically significant. The fact that the problems associated with sleep inertia immediately after the naps did not persist for more than 2 hours postnap was evident from an examination of the first RTSW (at 0210) which revealed greater alertness after both naps than after rest only.

Cognitive evaluation

Overall, performance suffered the most from sleep deprivation at the time at which mood and alertness decrements were most severe (in the midmorning hours). Prophylactic napping attenuated many of the problems, especially on tasks requiring vigilance and rapid responding. In addition, the zolpidem-induced nap tended to be superior to a "natural" nap.

Mood evaluation

Differences in vigor were most pronounced from 0500 to 0900 during the sleep deprivation period since these were the times when alertness suffered most under the no-nap condition. Differences in fatigue ratings occurred between the zolpidem nap and rest, with lower ratings after the zolpidem nap than after forced rest.

Conclusions

Zolpidem's rapid onset of action can be of significant benefit in situations where there is only a brief period available for sleep. When personnel have only 2 hours for a nap, zolpidem can maximize the effectiveness of that nap by rapidly inducing sleep. Although previous research indicates there are optimal times for napping, in the "real world" it may not be possible to schedule naps during these times. Work which must continue 24 hours a day with no breaks does not allow perfect scheduling of sleep breaks, so sleep must be taken when circumstances permit. When naps are possible but the timing is less than optimal, zolpidem decreases the time to sleep onset and leads to more time asleep during a restricted nap period. However, to minimize problems, individuals who plan to use zolpidem should pretest themselves in a safe environment where performance demands are not eminent, and allow enough time from awakening to avoid sleep inertia. In addition, whether zolpidem-induced naps or natural naps are used, care must be taken to avoid the temporary problems associated with postnap sleep inertia by allowing personnel sufficient time to fully awaken from naps prior to returning to work. Research is planned to determine what countermeasures may be used to more quickly alleviate sleep inertia. Also, when zolpidem tartrate is used to initiate a 2-hour prophylactic nap, there may be some minor effects until approximately 5.5 hours postdose, although the practical impact of these effects is probably negligible.

Acknowledgments

The opinions, interpretations, conclusions, and recommendations are those of the author and are not necessarily endorsed by the U.S. Army and/or the Department of Defense.

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Polyphasic Sleep and Napping Strategies

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Sleep deprivation is the most detrimental stressfactor for mental performance during continuous military operations. First of all it affects all subjective parameters such as well-being, mood state, motivation, creativity, care for others or social surplus. These changes are followed by alterations in psychometric performance tests such as vigilance tasks, with increasing number of omissions, complex tasks, cognitive functions, reduced reaction speed and learning capacity. When sleep is totally denied for several days more serious neurological symptoms appear such as slow motion, balance disturbance, nystagmus, headache, visual hallucination and sleep narcosis. All this symptoms are most apparent during night-time.

The amount of sleep necessary to prevent performance decrement in various tasks during continuous operations depends on the tasks to be done and the time of day. In addition there are big variations between individuals. Generally it is assumed that 1-2 hour of sleep each night is sufficient to avoid the most serious neurological symptoms during continuous operations lasting for approximately one week. If the mental function as expressed in the psychometric performance tests is to be preserved 2-4 hours of sleep may be necessary. If also the subjective parameters such as well-being, mood-state, motivation, creativity, are to be preserved almost normal sleep time is required. If the military operation is extended more sleep is needed at all levels to prevent performance decrement.

The experiment with the dancer running for the Guinness world record in marathon swing dance, showed that only 5 minutes of sleep each hour was sufficient to extend the dancers performance from 60 to 110 hours of continuous swing dance without severe neurological symptoms.

Use of hypnotics are very rarely necessary in sleep deprived subjects because they very easily fall asleep particularly during night time. In addition, hypnotics would also affect the subject's readiness. Amphetamine and similar drugs are stimulating the cerebral adrenergic neurotransmission leading to increased alertness for a certain period but followed by more pronounced exhaustion level afterward.

It is well documented that naps increase your performance or prevent further decrease during periods of sleep deprivation and in contrast to amphetamine naps restore mental function (Angus et al 1987, Opstad et al 1978). A question is how short a nap can be and still have restorative effect? For the dancer 5 minutes periods was demonstrated to be efficient. Even periods with micro-sleep that are almost impossible to avoid during prolonged periods with sleep deprivation may have a restorative effect. Even the hallucinations that have many similarities with dreams and sleep related cerebral activities may have restorative effects because the cadets rarely hallucinate on 2 consecutive nights. In addition the hallucinations are connected to the level of activation, since those cadets with high workload like the leaders do very rarely

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hallucinate. The typical cadets who hallucinate are a common member of the platoon that do not have any demanding tasks. The hallucinations are therefore more a blow-out preventer than a sign of pathology.

The problems with sleep inertia are in most cases short-lasting and can be overcome with high physical activities just after the sleep period. After 2 hours and 20 minutes sleep the cadets who had to run for 30 minutes had significantly better mental performance than those who were transported by lorry (Opstad et al unpublished). By overlearning the tasks that are going to be done immediately after the sleep period one might be able to keep a high physical work-load and by that reduce the sleep inertia period.

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ASSESSING THE ADAPTABILITY TO IRREGULAR REST-WORK RHYTHMS IN MILITARY PERSONNEL

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Operational decreases in performance resulting from sleep deprivation or irregular sleep-wake patterns are well known and are becoming increasingly important in today's industrialized society. Excessive sleepiness at unusual hours is estimated to affect approximately 5% of the general population and is associated with increased morbidity, loss of work hours, reduced productivity, increased work errors and impaired social and family relationship. In addition, there is an increased mortality risk when sleepiness affects motor vehicle and train drivers, aircraft pilots, nuclear power workers, and, generally, people involved in crucial occupations (e.g. Mittler, Carskadon, Czeisler, Dement, Dinges, Curtis, Graeber, 1988).

Military operations are often characterized by prolonged periods of wakefulness; irregular rest-activity patterns; long haul flights. These situations are unnatural. Severe sleep debt can accumulate, leading to dangerous levels of sleepiness and decreases of performance, which become evident after 24 hrs of sleep deprivation.

In addition, personnel involved in sustained/irregular operations are often unable to recognize and counteract fatigue and decreased performance. This condition can be due to: a) a discrepancy between subjective and objective decrease of vigilance; b) a tendency to underestimate fatigue; c) inadequate shift schedules; d) scarce attention to selecting people able to sustain prolonged wakefulness and/or unusual sleep-wake rhythms.

To maintain high levels of performance during sustained operation and/or irregular work hours, it is possible to adopt several non-pharmacological alertness management strategies aimed to:

a) optimize activity-rest schedules;

b) maintain adequate levels of vigilance and performance;

c) select people with the most useful psychological, psychophysiological, and chronobiological characteristics to adapt to work at unusual hours.

Optimize activity-rest schedules and maintain adequate levels of vigilance and performance.

Schedules implying night shifts and/or fragmentation of duty periods throughout the 24-hr day require meeting sleep need at different moments of the 24-hr continuum, until uninterrupted 8-hr sleep is possible. In such conditions, polyphasic sleep-wake strategies have potential practical applications. Sleep behaviour is considered polyphasic if less than 50% of total sleep time is obtained in one continuous episode. In such a situation, multiple naps and periods of wakefulness alternate throughout a 24-hr period (Stampi, 1992a). A large number of laboratory and field studies suggest that humans engaged in different types of polyphasic schedules can easily adapt to multiple napping regimens. It has been reported that some subjects can be able to reduce sleep to an average of less than 3 hours per day, up to 2 months. These were divided into 6 naps of 30 minutes each, one every 4 hours. Contrary to the usual findings of sleep deprivation experiments, in which only part of REM and stage 2 sleep,

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but not SWS amount are penalized, all sleep stages were proportionately reduced. This was probably due to the very long duration of the study (Stampi, 1992b).
With regard to performance, preliminary data seem to show that individuals under polyphasic and ultrashort sleep schedules can function at levels equal to, or higher than, when they were under a comparable amount of monophasic sleep (Stampi, 1992c). It appears that polyphasic sleep-wake schedules are a viable solution in oreder to maintain high levels of efficiency during continuous work situations.
For the armed defence service on air bases, the Italian Air Force adopts, an unusual work schedule, characterized by 24-hrs on duty followed by a day off duty. The day on duty is characterized by 4 rest-activity cycles repeated throughout the day. Each cycle is of 2-hrs of activity and 4-hrs of rest (sleep allowed).
In a previous study (Porcù, Casagrande, Ferrara, Bellatreccia, 1998) Italian armed defence personnel were monitored by means of ambulatory polysomnography while attending their 24-hr rest-activity schedule. Sleep periods were visually scored according to standard criteria. Wake periods were visually scored using both 30 sec and 5 sec epochs in order to reveal episodes of drowsiness and/or microsleep. Results showed that total sleep time was substantially reduced as compared to the usual 7-8 hour monophasic nocturnal sleep. Subjects did not sleep during the first rest period (11.00-15.00). Time in sleep linearly increased in the course of the 3 remaining rest periods. Normal sleep structure was anyway substantially maintained. SWS and REM sleep were mostly expressed, respectively, in the first (3rd rest cycle: 9.00 p.m. - 1.00 a.m.) and in the last (4th rest cycle: 3.00-7.00 a.m.) third of the night, maintaining their own natural circadian rhythm.
In addition, our results indicate that this rest-activity schedule, despite the considerable sleep reduction, allowed maintaining good levels of vigilance as shown by the virtual absence of EEG microsleeps.
Thus, results of this study confirm that it is easy to break the usual monophasic sleep efficiency and to adapt to a complicated regimen, alternating 24 hrs of an usual rest-activity cycle with a nocturnal monophasic sleep and 24 hrs of a polyphasic pattern. However, these data do not allow to draw any conclusion about performance, since it was not evaluated in the present study. The great reduction of sleep duration did not cause any evident decrease of vigilance, as defined by the occurrence of microsleeps, but we cannot exclude that the very great sleep loss also did not cause detrimental effects on performance. Whether future research will prove that adult humans can adapt to this schedule with no significant decrease of performance, this alternating monophasic-polyphasic regimen should be a suitable strategy for the management of continuous operations.

Select people with the most useful psychological, psychophysiological, and chronobiological characteristics to adapt to work at unusual hours.

Although sleep deprivation, time of day and time on task are considered among the most important causal factors of daytime sleepiness (e.g. Åkerstedt and Kecklund, 1994), the levels of vigilance may still significantly vary according to individual differences. Some individual characteristics contribute, in fact, in modulating general levels and time of day effects of vigilance, sleepiness and performance and modulate even the intensity with which the various deactivating factors individually act (e.g. Åkerstedt and Torsvall, 1981; Harma, 1993).
Verifying whether and to what extent some stable individual differences are associated to specific variations of vigilance and performance may be important in orienting the best criteria for the selection of personnel involved in particular types of professions requiring shift work, prolonged activity for many hours or unusual hours, and/or monotonous activity.
Poor attention has been paid to such important factors as the individual ones. In

fact, there is a surprising lack of studies on individual differences in the adaptability to irregular sleep-wake rhythms.
Many factors have contributed to this condition. Studies on individual differences are necessarily long, time consuming and require a large sample size.
To find out which individual characteristics can garantee the best adaptability to sustained operations and to irregular or unusual rest-activity schedules, it is essential to define:
a) Which physiological, behavioral and/or psychological parameters are useful to define the "adaptability dimension".
b) Which individual traits can allow us to predict adequate adaptability.
To evaluate both the "adaptability construct" and the "individual traits", it is necessary to take into account a very large number of variables: psychological, subjective, behavioral, physiological/biological, psychophysiological, chronobiological.
It is also necessary to use a multivariate statistical approach:
a) Factor Analysis, Discriminant Analysis, and/or Cluster Analysis to single out the parameters (and their weight) that contribute to define the "adaptability construct";
b) Multiple Regression Analysis to evaluate the predictors of adaptability;
c) Multivariate Regression Analysis for evaluating the specific contribution of several "predictors" (independent variables) on several "criteria" (dependent variables).
To carry out such statistical analysis it is necessary to have a huge subject sample. It is estimated that about 12 observations are needed for each considered variable.
Studies of this size can hardly be carried out by a single laboratory. A multicentric approach is necessary:
a) several laboratories (nations) should participate to a common "core project;
b) the same experimental design should be followed in each laboratory;
c) the subject sample size should be shared by the participants;
d) each country might add original contributions to the project, integrating the "core project
Here follows a summary of a research project, which we propose to carry out on personnel working on polyphasic-rest activity schedules, in order to address the above issues.

Research project.

<u>Subject inclusion criteria</u>
- Healthy males
- Age: 18-40 years old
- No sleep disorders in the anamnesis
- No previous significant shift-work/irregular sleep-wake experience
- No drugs/alcohol
- Normal lifestyle

<u>Experimental design</u>
The project is divided into 4 phases:
- Phase one, immediately before the beginning of the polyphasic activity, to be carried out in the lab;
- Phase two and three, during the polyphasic activity, to be carried out "in the field";
- Phase four, during the polyphasic activity, to be carried out in the lab on subjects with extreme individual characteristics, selected on the basis of the results of the three previous phases.

PHASE 1 (Before the polyphasic activity)

a) <u>Questionnaires will be used to evaluate of the following individual traits:</u>

- Sleepiness: Epworth Sleepiness Scale (ESS, Johns, 1991);
- Circadian Typology: Morningness-Eveningness Questionnaire (Horne & Ostberg, 1976);
- Extroversion, Neuroticism, Psychoticism: Eysenck Personality Inventory (EPI, Eysenck, 1967);
- Coping Strategies: Coping Inventory for Stressful Situations (CISS, Endler e Parker, 1990);

• Sleep, Vigilance and Sleep-Wake Cycle Characteristics (Questionnaire by the Italian Air Force).

b) Laboratory evaluation of:

• Standard polygrafic recordings of sleep for two nights;
• Diurnal and nocturnal administrations of MSLT and MWT;
• Diurnal and nocturnal repeated assessments of vigilance, performance and mood (mainly by means of EEG measures, "pencil-and-paper" and/or computerized task;

c) Biological parameter assessment:

• Multiple salivary samples to evaluate melatonin and cortisol rhythms;
• Continuous recording of body temperature;
• Multiple blood samples to evaluate parasympathetic and orthosympathetic hormones, as well as lymphocyte benzodiazepine receptors;
• EKG recording and heart rate spectral analysis;

PHASE 2 (After 1 month of polyphasic activity)

"In the field" recordings, 4 consecutive days (2 days on duty, 2 days off duty):
• Ambulatory polysomnography (96 hrs);
• Reaction Time Task to weak vibratory stimuli (96 hrs);
• Letter Cancellation Tasks (Casagrande, Violani, Curcio, Bertini, 1997) and subjective evaluations of mood and alertness as follows:
• DAY ON DUTY: before and after each rest period;
• DAY OFF DUTY: upon morning awakening, at the same time of the day on duty, immediately before "lights off";
• Sleep logs as follows:
• DAY ON DUTY: a brief questionnaire on the sleep-wake cycle and vigilance filled in after each of the 4 rest periods;;
• DAY OFF DUTY: a brief questionnaire on the sleep-wake cycle and vigilance filled in upon morning awakening.
• Photostimulation: blind counterbalanced administration of bright and dim light as follows:
• 10 min stimulation after each of the 4 rest periods (immediately before working);
• 30 min stimulation at the end of the working day (i.e. in the morning of the day off duty).

PHASE 3 (After 6 months of polyphasic activity)

The same experimental design as in PHASE 2 will be followed, in order to assess possible changes in the considered variables due to an improved adaptation to the irregular rest-work schedule

PHASE 4 (After 8 months of polyphasic activity)

The same experimental design as in PHASE 1 will be followed, on groups of subjects selected for their "extreme" characteristics of adaptability to the irregular rest-work schedule (i.e. the best and worst adapted subjects).

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Analysis of Heart Rate Variability during Sleep as a Tool for Assessment of Cardiovascular Adaptability and Fatigue in Sleep-Wake Cycle

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Summary

An assessment of general adaptation reserve of cardiovascular function by means of heart rate (HR) and HR variability analysis during sleep and functional tests is demonstrated. A possibility to evaluate a restoration of cardiovascular reserve after sleep by means of HR changes during active orthostatic test is shown. The level of autonomic HR control and balance of sympathetic-parasympathetic inputs might be measured by means of analysis of HR power spectrum main oscillatory components. The differences in cardiovascular reserve of healthy subjects and cardiac patients, as well as possibility of HR restoration during sleep was demonstrated. *In conclusion.* Adaptability of cardiovascular function and fatigue–restoration cycle might be assessed by means of very simple methodology – an analysis of HR Poincare maps. Its practical application in the cases of fatigue, developed during disturbed wake-sleep cycle or overtraining situation in high physical or emotional overcrowding is shown.

INTRODUCTION

Evaluation of cardiovascular adaptability e.g. cardiovascular functional reserve, as well as evaluation of fatigue, might be seen as very important aspects in organization of day-night activities for military staff (at home and fight missions) and for appropriate work of civil operators, especially in the cases of shift work or disturbed sleep-wake cycle.

Autonomic control of cardiovascular function, being a main adaptability definitive characteristic, consists of two main components, tonic and reflex autonomic control [2, 11]. Tonic control of cardiac function might be assessed by a measurement of heart rate (HR) variability at rest, while reflex control was ascribed by several HR responses to tests, involving exercise or shifts of sleep stages, related to baroreflex control [2, 6, 9, 10, 11, 16]. Between of the tests might be mentioned an active orthostatic test (AOT), submaximal or symptom limited exercise, medicamental tests, as well as sleep with a natural changes of autonomic control during shifts of sleep stages and cycles [6, 17, 20, 21].

Night sleep with modifications in functional state of autonomic nervous system during shifts of sleep stages and cycles is responsible for modification of HR variability and its periodical structure, reflecting particular domination of sympathetic or parasympathetic control at individual sleep stage [1, 7, 8, 13, 15, 19, 20, 21]. From the other hand, normal sleep was responsible for restoration of functional state of nervous system, regulating all organism functions, particularly of cardiovascular function, after of their activation or exhaustion during daily activities or mission action.

Working hypothesis is that assessment of HR frequency and variability changes during night sleep and functional tests (exercise, AOT) might be used as a measure of adaptability of cardiovascular system e.g. for evaluation of fatigue or restoration after it in healthy subjects (H Ss) or cardiac patients.

The goal of the study was an assessment of general adaptation reserve of cardiovascular function by means of HR analysis during sleep and functional tests, as well as a demonstration of possibility to evaluate a restoration of cardiovascular reserve during sleep by means of HR changes during active orthostatic tests, performed just before and after sleep.

METHODS

Computerized analysis of HR frequency and variability in parallel to hemodynamics (measured by impedance cardiography) was performed during night

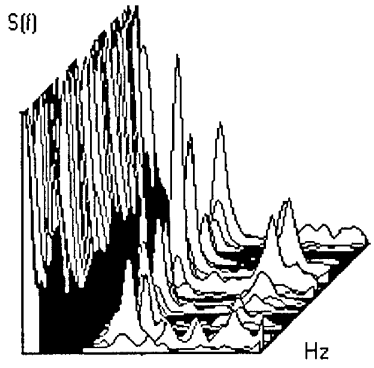

Fig. 1. An example of HR running spectra during individual night sleep stages.

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sleep and functional tests such as active orthostatic test at day-time, evening-time and morning-time, as well as, during exercise, using bicycle-ergometry test, reaching submaximal HR frequency or symptoms limiting exercise. Sleep stages and cycles have been identified using conventional polysomnography. HR power spectrum by means of Furje analysis, including running spectra (Fig. 1) was used for identification of three main oscillatory components: very low frequency component (VLFC), related humoral control, low frequency component (LFC), due to more sympathetic one, and high frequency component (HFC), reflecting parasympathetic control [3, 12, 18, 19].

For evaluation of total cardiovascular reserve was used a simple methodology of non-linear dynamic – Poincare map (or return map) of HR with analysis of relationship between of consecutive interbeat intervals (RR_i and RR_{i+n} sequence, while n = 1), recorded during shifts of sleep stages and cycles, as well as during active orthostatic test, or increasing physical exercise, or all of them collected together (Fig. 2).

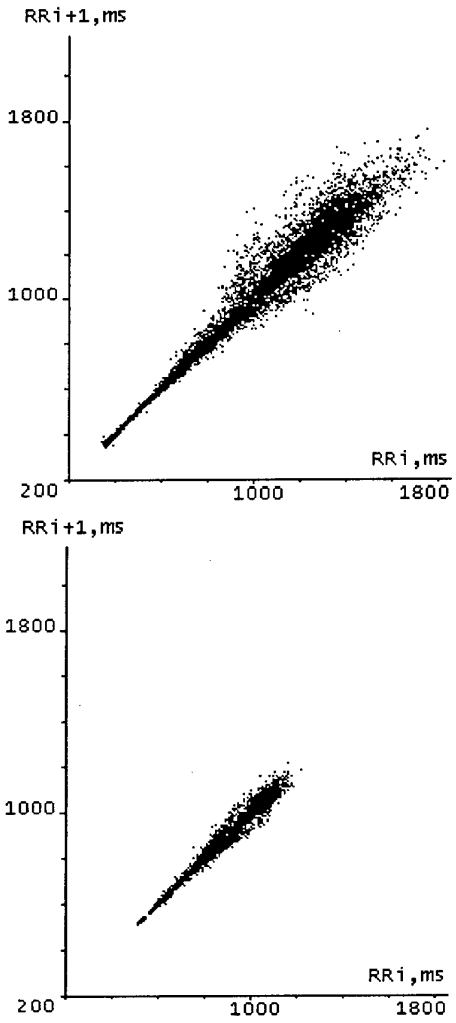

Fig. 2. An examples of Poincare maps of RR intervals, collated during sleep and exercise test in healthy Ss (top) and IHD pt (bottom).

The contingent was 40 H Ss and 153 ischemic heart disease patients (IHD pts). H Ss and IHD pts were distributed into the subgroups according to HR frequency baseline level at rest during waking state just before sleep (RR < 1.0 s, RR ≥ 1.0 s). IHD pts were distributed also according to their HR responses to sleep stages: typical (the same as for H Ss) and reduced HR responses to shifts of sleep stages (HR responses less than 5% from baseline level).

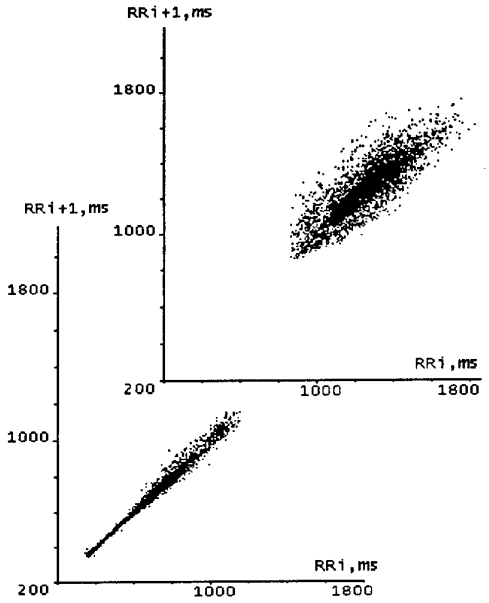

Fig. 3A. An examples of Poincare maps of RR intervals during sleep (top) and exercise (bottom) in healthy Ss.

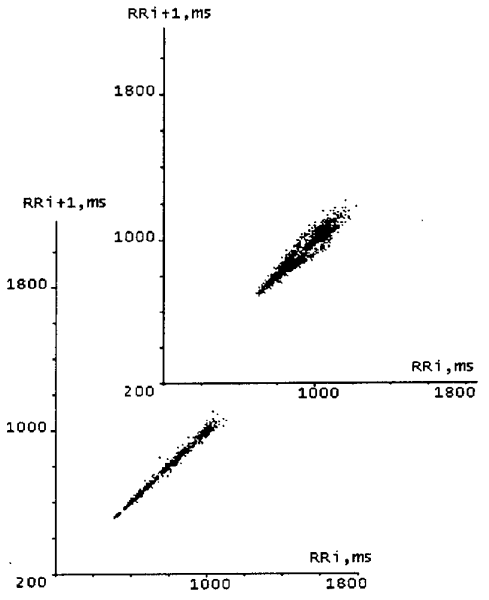

Fig. 3B. An examples of Poincare maps of RR intervals during sleep (top panel) and exercise (bottom) in IHD pts.

RESULTS AND DISCUSSION

Adaptability of cardiovascular function

HR frequency and HR variability at rest might be seen as reflecting prevalence of sympathetic or parasympathetic HR control, while maximal HR responses to all tests (sleep stages and exercise) were reflecting a total level of HR adaptation reserve for particular subject at a current its functional state Figure 2 demonstrates significant difference between of prevalence of parasympathetic HR control at rest (maximal HR variability during night sleep) for H Ss and IHD pts.

From the other hand, Poincare maps, presented in Figure 2, reflect maximal level of HR frequency changes during all tests, which might be used as a measure of adaptability. It was much more expressed for H Ss (ΔRR = 1400 ms): between of minimal HR value during slow wave sleep (RR ≅ 1750 ms) and maximal one during peak exercise (RR ≅ 350 ms). For IHD pts its total level of adaptability was twice as low (700 ms), HR being less low at minimal level during sleep (1200 ms) and less high at maximal one during exercise (500 ms). Thus, reduction of HR maximal response in IHD pts might be

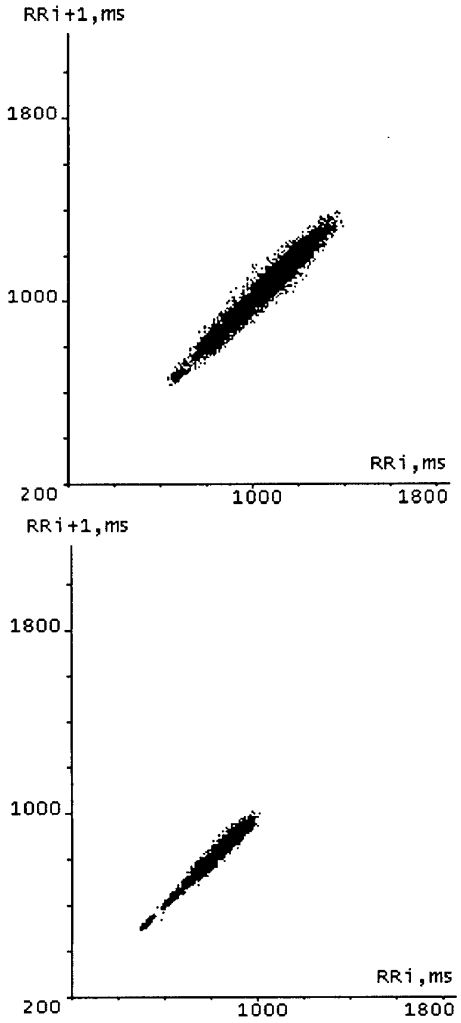

Fig. 4. An examples of Poincare maps of RR intervals, collated during sleep and exercise test in IHD patient with leading hypertension (top) and patient with leading congestive heart failure (bottom).

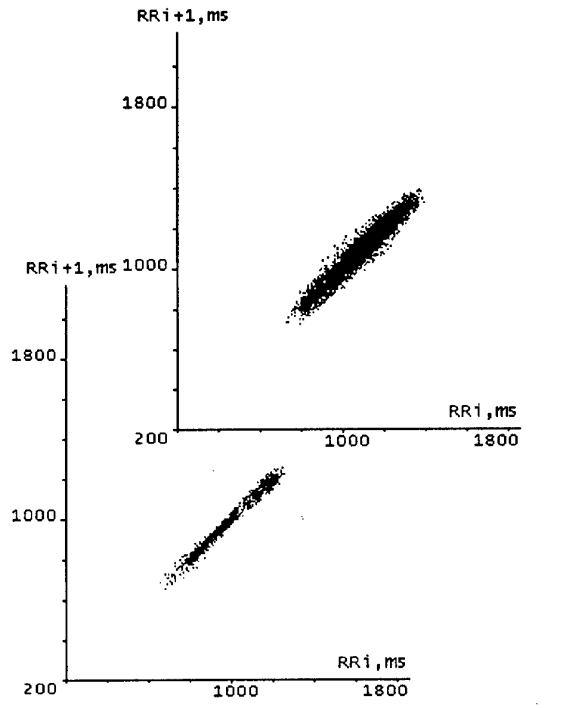

Fig. 5A. An examples of Poincare maps of RR intervals during sleep top panel) and exercise (bottom) in IHD pt.

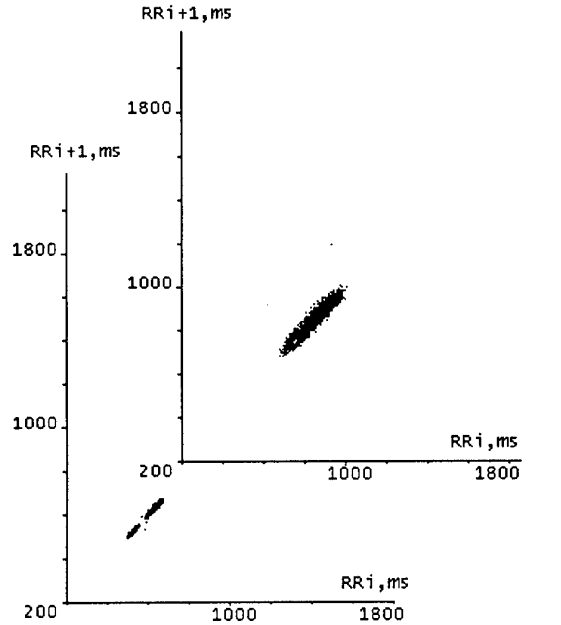

Fig. 5B. An examples of Poincare maps of RR intervals during sleep (top panel) and exercise (bottom) in IHD pt.

related to reduction of HR control from both sides, parasympathetic and sympathetic control.

Figure 3 demonstrates an evaluation of HR adaptability reserve for H Ss (Fig. 3A) and IHD pts (Fig. 3B), while HR recording used during sleep only (top panel) and during waking rest–exercise only (bottom). In both situations of testing H Ss demonstrated more wide adaptability reserve than IHD pts. For H Ss it was more expressed during sleep than during exercise, while in IHD pts this difference shown opposite direction – it was lower in sleep, demonstrating reduction of central parasympathetic control.

Figure 4 demonstrates the differences of HR adaptability reserve in two IHD pts with the same NYHA functional class: the patient with leading hypertension (top panels of Fig. 4 and Fig. 5A) shown more wide adaptability reserve, than patient with congestive heart failure after myocardial infarction, having reduced HR response during the shifts of sleep stages and exercise test: ΔRR with of 900 ms in the first one and 450 ms in the second one, correspondingly. If evaluated separately HR adaptation reserve was more high during sleep (ΔRR ≅ 600 ms) than exercise (ΔRR ≅ 400 ms) for the first patient, while opposite situation was for the second one (ΔRR ≅ 300 ms during sleep and ΔRR ≅ 400 ms during exercise). From the other hand, HR frequencies in sleep and exercise were not overlapping, as it was seen for H Ss and for the rest of the patients with congestive heart failure.

Thus, evaluation of adaptability of cardiovascular function, while measured as total HR responses during sleep and exercise should provide important information about the functional reserve of investigated persons. Although, while measured separately during night sleep and functional tests at waking state, Poincare maps might dispose a supplementary information, about the which branch, sympathetic or parasympathetic, of HR control was more involved in to the process of adaptation.

Restoration of Cardiovascular Function during Sleep

In the cases of fatigue, developing during disturbed wake-sleep cycle or overtraining situation in high physical or emotional overcrowding, as well as, it is in IHD pts due to complications, there might be some differences in HR control restoration during sleep. If cardiovascular function was not able to restore, a fatigue might be increasing during the rest of the day. Such situations might be seen in sportsmen during their training sessions while overstrained [4, 5, 22]. Because of that HR response to AOT were used for evaluation of restoration of their functional status after night sleep [14].

The same methodology was shown as demonstrating positive results for investigation of HR restoration during sleep in IHD pts. Figure 6A demonstrates an increase of HR responses to AOT at morning hours just after sleep (top panel) as compared to day time AOT (bottom) and evening-time (middle panel)

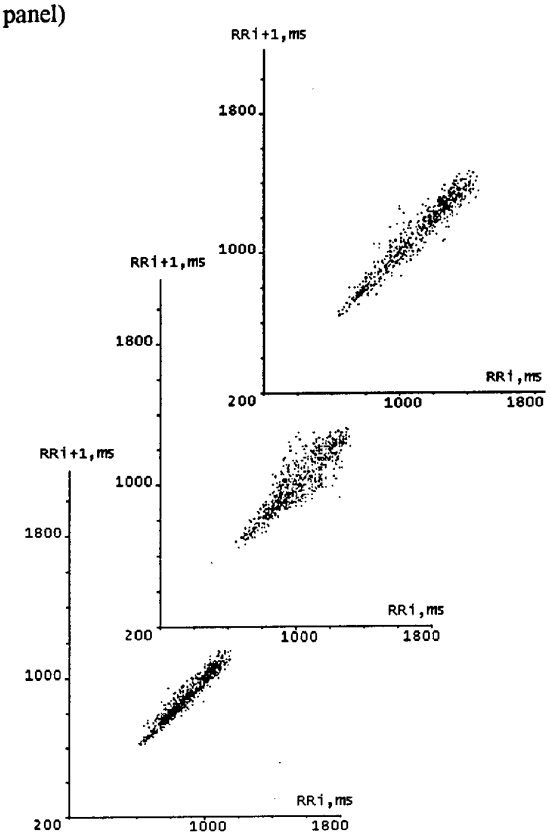

Fig. 6A. An examples of Poincare maps of HR during AOT tests, performed at day-time (bottom), evening-time (middle) and morning-time (top panel) in H Ss.

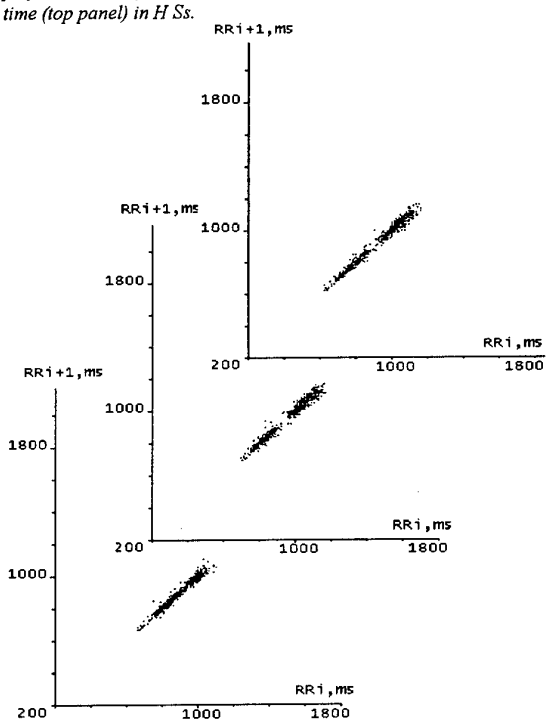

Fig. 6B. An examples of Poincare maps of during AOT tests, performed at day-time (bottom), evening-time (middle) and morning-time (top panel) in IHD pt.

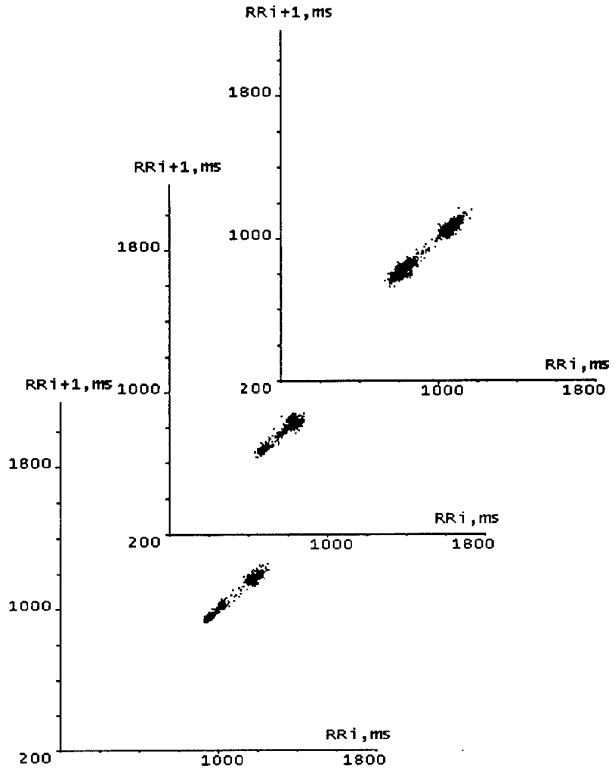

Fig. 7A. An examples of Poincare maps of HR during AOT tests, performed at day-time (bottom), evening-time (middle) and morning-time (top panel) for IHD pt.

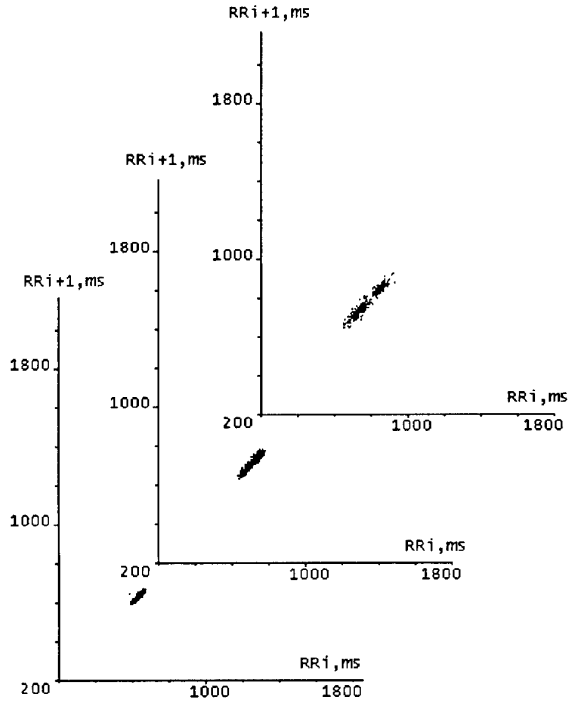

Fig. 7B. An examples of Poincare maps of HR during AOT tests, performed at day-time (bottom), evening-time (middle) and morning-time (top panel) for IHD pt.

for H Ss. The same tendency of HR responses changes were demonstrated for IHD pt (Fig. 6B), although HR changes were less expressed.

The difference of HR restoration after sleep in two IHD pts (shown in Fig. 4) demonstrated some specific differences (Fig. 7A, 7B). In IHD patient HR response to AOT at evening-time was reduced as compared to day-time, although restored after sleep (Fig. 7A). However, in IHD patient with more reduced adaptability reserve (Fig. 7B), despite of very small response of HR to AOT at day-time, a tendency for restoration of HR response after sleep there was still present.

Table 1 demonstrates HR frequency and variability dynamics during sleep, if compared at the first and the last cycles of sleep: there were seen the clear-cut differences of the level of decrease of HR frequency and an increase of HR variability during sleep in relation to initial HR, HR decrease during night was significant only in those with initially increased HR either for H Ss and IHD pts. HR variability changes were related positively to their initial level.

A tendency of negative relationship to baseline HR might be seen in HR changes, while measured just before and after sleep (Table 2). It was true for H Ss and IHD pts, although only for those with typical HR response to night sleep. Although for IHD pts with reduced HR response to sleep there was no differences of HR responses, as compared HR just before and after sleep in the cases with slight prevalence of HR sympathetic control. It was followed by a reduction of HR maximal response to AOT, instead of its increase, as it was in H Ss and total IHD pts group. If initial bradycardia is present in IHD pts with reduced HR pattern during sleep it was followed by non-significant decrease of HR frequency, but increased HR maximal HR response to AOT, being opposite as compared to typical group of IHD pts.

Table 1. *Characteristics of HR frequency and variability during the first and the last cycles of sleep in healthy subjects and IHD pts*

	First cycle		Last cycle	
	RR, ms	σRR, ms	RR, ms	σRR, ms
Healthy Ss	1093	65	1129	79
RR<1.0 s	954	54	1113	69
RR≥1.0 s	1177	72	1145	86
IHD pts	1026	42	1037	48
RR<1.0 s	934	38	1027	43
RR≥1.0 s	1132	47	1051	54
HRSP typical	1022	52	1051	61
RR<1.0 s	946	49	1042	55
RR≥1.0 s	1098	56	1069	67
HRSP reduced	1032	31	1028	34
RR<1.0 s	906	26	1007	27
RR≥1.0 s	1178	36	1075	41

Thus, an analysis of HR responses to AOT during day activities and just before and after sleep might be

important measure of fatigue during a day time and ability of cardiovascular control restoration after sleep. Composition from restoration of HR and hemodynamics control during sleep might be used for creation of more full picture of restoration during sleep either in H Ss and IHD pts. For the latter hemodynamics changes were more important [14, 18, 22], than for H Ss in whom adaptation reserve of cardiovascular system is present and working through autonomic HR control mainly.

Table 2. HR responses to AOT, recorded at day-time, evening-time and morning-time after sleep in healthy Ss and IHD pts

	RR_I, ms	RR_B, ms	ΔRR_B, ms	ΔRR_B, %
		Day-time		
Healthy Ss	980	620	360	36
RR<1.0 s	898	576	304	34
RR≥1.0 s	1053	657	406	38
IHD pts	958	718	248	25
RR<1.0 s	911	664	227	25
RR≥1.0 s	1042	775	271	26
HRSP typical	965	653	281	31
RR<1.0 s	913	621	268	31
RR≥1.0 s	981	691	295	31
HRSP reduced	953	783	186	18
RR<1.0 s	879	693	165	18
RR≥1.0 s	1155	858	204	18
		Evening-time		
Healthy Ss	1085	673	409	37
RR<1.0 s	879	570	309	34
RR≥1.0 s	1144	705	439	38
IHD pts	980	689	301	31
RR<1.0 s	859	617	246	29
RR≥1.0 s	1111	754	350	33
HRSP typical	1017	650	342	33
RR<1.0 s	866	639	261	25
RR≥1.0 s	1065	656	409	37
HRSP reduced	1009	732	295	29
RR<1.0 s	954	609	225	26
RR≥1.0 s	1153	793	330	31
		Morning-time		
Healthy Ss	1082	608	479	43
RR<1.0 s	991	597	394	39
RR≥1.0 s	1123	612	505	44
IHD pts	981	676	323	32
RR<1.0 s	902	636	260	29
RR≥1.0 s	1090	711	379	34
HRSP typical	1004	655	297	31
RR<1.0 s	919	632	265	30
RR≥1.0 s	993	670	323	32
HRSP reduced	1010	671	342	32
RR<1.0 s	954	620	202	24
RR≥1.0 s	1176	703	412	37

CONCLUSIONS

The level of autonomic HR control and balance of sympathetic-parasympathetic inputs might be measured by means of analysis of HR power spectrum components. Adaptability of cardiovascular function and fatigue–restoration cycle might be assessed by means of very simple methodology – an analysis of HR Poincare maps, constructed from consecutive RR intervals, recorded during sleep, exercise, or active orthostatic tests. All tests together enable to evaluated a total level of adaptation reserve of cardiovascular function, using HR responses to all tests. Particular restoration of adaptability, might be evaluated using HR analysis during repetitive active orthostatic tests, performed just before and after sleep.

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14. Abstract

These proceedings include the Technical Evaluation Report, two Keynote Addresses and 20 solicited papers of the Workshop sponsored by the NATO Human Factors and Medicine Panel and held at the Scuola Navale Militare "Francesco Morosini" in Venice, Italy, from 3-4 June 1999.

NATO Contingency Operations provide new challenges to military personnel's health, safety and performance. In fact, these operations are commonly characterized by the need for effective performance at any time of the day or night.

There is a growing body of knowledge pointing to the existence of important individual psychophysiological differences that may enable some individuals to better adapt to irregular rest-work rhythms. Furthermore, selected categories of drugs may be employed in operational conditions. The purpose of this Workshop was to address both the individual difference implications during irregular sleep-wake regimens and the state of the art in the pharmacological management of sleep-wake rhythms.

The papers addressed the individual difference implications in: a) sustained and continuous operations; b) flash adaptation to shift work and to new time zones; c) tendency to fall asleep; d) sleep deprivation; e) polyphasic rest-work schedules and napping strategies; f) sleep inertia. In addition, the papers also addressed the usefulness in operational settings of: a) bright light therapy; b) melatonin therapy; c) hypnotics to promote sleep; d) stimulants to sustain performance.

These proceedings will be of interest to those who are concerned with the sleep-wake management of personnel in air, sea and land operations; to aerospace scientists, as well as to people working in the field of applied sleep research, wanting an updated review of relevant research in the field of individual difference implications and the pharmacological/non-pharmacological management of irregular rest-work schedules.

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